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Mortality in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

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ABSTRACT (278 words)

Objective: To compare mortality in chronic kidney disease stages 4 or 5, peritoneal dialysis, hemodialysis, and transplanted patients.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Swedish adult patients with chronic kidney disease stage 4 or 5 (n=3040; mean age 66y), peritoneal dialysis (n=725; 60y), hemodialysis (n=1791; 62y), and renal transplantation (n=606; 48y) were identified in Stockholm County clinical quality registers for renal disease between 1999 and 2010. Five general population controls were matched to each patient by age, sex, and index year.

Exposure: Chronic kidney disease status (stage 4 or 5/peritoneal dialysis/hemodialysis/ transplanted)

Primary Outcome: All cause mortality ascertained from the Swedish Causes of Death Register. Mortality hazard ratios were estimated using Cox regression conditioned on age, sex, diabetes status, education level, and index year.

Results: During 6553 person-years 766 patients with chronic kidney disease stage 4 or 5 died (deaths/100 person-years 12, 95%CI 11-13) compared with 186 deaths during 1113 person-years in peritoneal dialysis (17, 95%CI 15-19), 924 deaths during 3680 person-years in hemodialysis (25, 95%CI 23-27), and 53 deaths during 2935 person-years in transplanted patients (1.8, 95%CI 1.4-2.4). Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.2-4.0) for chronic kidney disease, 5.6 (95%CI 3.5-8.9) for transplanted patients, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis. In direct comparison versus chronic kidney disease, the mortality hazard ratio was 1.7 (95%CI 1.4-2.1) for peritoneal dialysis, 2.6 (95%CI 2.3-2.9) for hemodialysis, and 0.5 (95%CI 0.3-0.7) for transplanted patients.

Conclusion: Patients with chronic kidney disease stage 4 or 5 had considerably lower mortality risk than dialysis patients, and considerably higher risk than transplanted patients and the general population.

ARTICLE FOCUS

- Chronic kidney disease and renal replacement therapy are associated with increased mortality
- Some studies suggest mortality in chronic kidney disease stage 4 and 5 to approach dialysis mortality rates
- No studies have compared mortality in chronic kidney disease, in different forms of dialysis, and after transplantation with the general population, and directly with each other

KEY MESSAGES

- Relative mortality risk versus matched general population controls was 4 in chronic kidney disease, 6 in transplanted patients, 9 in peritoneal dialysis and 13 in hemodialysis patients
- In direct comparison versus chronic kidney disease patients, relative mortality risk was 0.5 in transplanted patients, 1.7 in peritoneal dialysis, and 2.6 in hemodialysis
- The markedly increased mortality observed in both peritoneal dialysis and hemodialysis suggests that such therapies should not be started too early

STRENGTHS & LIMITATIONS

- This study was population-based with no restrictions regarding comorbidities or demography, and data were collected in routine clinical care to which there is universal access in Sweden
- Using the unique personal identity number of each Swedish resident, follow-up was complete regarding mortality
- Although all renal replacement therapy patients in the catchment area were included, an unknown number of chronic kidney disease stage 4 and 5 patients were likely missed, as the condition is underdiagnosed
- Direct comparison of mortality across different health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the chronic kidney disease health state

INTRODUCTION

Mortality is substantially elevated in chronic kidney disease (CKD) and dialysis patients,[1-3] with some studies describing CKD patients in stages 4 and 5 as having mortality rates approaching the rates in dialysis.[1] However, there are no studies directly quantifying the relative mortality in CKD, dialysis (separating peritoneal and hemodialysis), and transplanted patients.

An analysis of an insured US population found patients in CKD stages 4 and 5 to approach dialysis mortality rates with a 3- and 6-fold higher mortality risk, respectively, than patients with an estimated glomerular filtration rate (eGFR) ≥60.[1] This can be compared with a standardised mortality ratio of 8 reported in Swedish incident CKD patients stages 4 and 5 followed for up to almost 7 years,[2] and with hazard ratios ranging from 3.7 to 7.0 for stage 4 patients (eGFR 15-29) with varying levels of albumin-to-creatinine-ratio in a meta-analysis of more than 100,000 patients, using patients with an eGFR of 90-104 as reference.[4]

Regarding dialysis mortality, a large European study showed an 8-fold higher age-standardised mortality due to both cardiovascular and non-cardiovascular death compared to the general population.[3] The study did not distinguish between peritoneal dialysis and hemodialysis.

These US and European studies indicate that mortality in CKD stages 4 and 5 may be as high as in dialysis. However, control groups differed between the studies (patients with normal kidney function defined as eGFR ≥60[1] or 90-104[4]; aggregated Swedish[2] or European life tables[3]), and mortality may differ between modes of dialysis.[5]

The aim of this population-based cohort study was to examine mortality in CKD stages 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients in relation to matched general population controls, and directly with each other.

METHODS

This population-based cohort study was performed in the Swedish health care system using patient data from clinical quality registers kept for quality of care evaluation in Stockholm County. These data sources were combined with matched general population controls, and enriched with outcome and exposure data via linkage to nationwide health registers kept by the National Board of Health & Welfare and demographic registers at Statistics Sweden. Register linkage was performed using the unique personal identity number assigned to each Swedish resident.[6] Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 9.4 million on December 31, 2010 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 2.1 million inhabitants, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, and patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient hospital care.[7] Care for CKD patients was a mix of mainly outpatient hospital and primary care, while there was also an unknown number of undetected patients. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[8] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[9] and the corresponding European guidelines.[10]

Quality Register Sources

CKD Patients: Data from the Stockholm County CKD Register were used, including adult CKD patients in stages 4 and 5 not on dialysis from Karolinska and Danderyd University Hospital from 1999 to 2010. Stages 4 and 5 were defined as an eGFR of 15-29 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[11]

Renal Replacement Therapy Patients: Data on dialysis initiation, type of dialysis, and transplantation were collected from the Swedish Register of Renal Replacement Therapy, including all adult patients on renal replacement therapy in Stockholm County.[12 13]

The National Patient Register

Data on inpatient and outpatient hospital care were retrieved from the Swedish National Patient Register.[14] This register contains the personal identity number, visit/admission date (and discharge date for inpatients), and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10). The register reached national coverage in 1987 for inpatient care, and the outpatient component was added in 2001.

From inpatient and outpatient care registered in the National Patient Register, data on hospital visits listing diabetes, malignancies, circulatory disease, and chronic obstructive pulmonary disease were gathered. Visits listing these diagnoses were searched for during the last ten years (ICD-9 and ICD-10 codes provided in **eTable 1**).

Matched General Population Control Cohort

From the Register of the Total Population at Statistics Sweden, five general population controls were matched to each patient at the time of inclusion into the CKD register, and renal replacement therapy initiation, using age (+/-1 year), sex, and index year as matching factors. Data on place of residence, emigration status, and highest attained education (available for patients <75 years) were also retrieved from Statistics Sweden.

Outcome and Follow-Up

The primary outcome was all cause mortality. Secondary outcomes for CKD patients included initiation of renal replacement therapy and the composite outcome death or dialysis.

Dates and causes of death were retrieved from the Causes of Death Register kept by the National Board of Health and Welfare. Dates of death were available until July 31, 2010, while main and contributory death causes were available until December 31, 2008.

CKD and renal replacement therapy patients included from January 1, 1999, were analysed. Follow-up started at date of inclusion into the Stockholm CKD Register, dialysis initiation, or transplantation. Patients accrued person-time in a specific health state until death, transition to another health state, emigration, or July 31, 2010, whichever came first.

Statistical Analysis

Unadjusted incidence rates and Kaplan-Meier curves were used to present absolute risks. For CKD patients, a Cox proportional hazards model was used to model time to dialysis, and the composite outcome death or dialysis. The models were adjusted for age, sex, education level (≤9, 10-12, >12 years, missing), baseline eGFR (stage 4 versus 5), and comorbidity status, and index year.

Comparison versus the General Population: In mortality analyses versus matched general population controls, Cox models conditioned on age, sex, education level, diabetes status, and index year were used. Some patients did not have a full five controls, but were still included in the analyses, while patients with no controls were excluded. For dialysis and transplanted patients the Andersen-Gill[15] method was applied allowing for patients to re-enter a health state after exiting.

In order to investigate whether potential differences in all-cause mortality were driven by cardiovascular mortality, sensitivity analyses were performed for cardiovascular as well as non-cardiovascular deaths. An analysis was also performed to compare mortality by education level.

Direct Comparison of CKD versus Renal Replacement Therapy: To directly compare mortality in the different health states, a Cox model conditioned on age, sex, education level, diabetes status, and index year was used with health state as primary predictor.

Missing data on education level were handled using the missing indicator method. Data were complete on age, sex, and register-determined comorbidity status. Missing baseline eGFR resulted in exclusion from CKD analyses.

Statistical analyses were performed using SAS (version 9.3) and Stata (version 11). All P-values are two-sided and P-values <.05 were considered statistically significant.

RESULTS

A total of 4249 patients were included. Follow-up of mortality was complete and all patients were analysed, except for 19 CKD patients who were excluded due to missing baseline eGFR.

Patient characteristics at inclusion, dialysis initiation and transplantation are shown in **Table 1**. CKD patients were on average 66 years old at inclusion, while dialysis patients were younger, and transplanted patients much younger: 48% of CKD patients were more than 70 years old, compared to 37% of hemodialysis, 28% of peritoneal dialysis, and 0% of the transplanted patients. All groups were predominantly male, and the education level was broadly similar to that in the general population.

Regarding selected register-identified comorbidities, the CKD and dialysis patients were similar, while the younger transplanted group displayed much lower prevalence. More than 30% of patients (except the transplanted group) had diabetes, compared to 3-7% in the matched general population (**eTable 2**). Approximately 80% of patients had circulatory disease history at inclusion, with about 10% having had myocardial infarction and 10% stroke (except transplanted patients). In CKD and dialysis patients malignancies were also more common than in the general population.

In the CKD cohort at inclusion, the mean eGFR was 18 (SD 6; median 18; range 4.1-29.9). A third (n=999) had values <15, while 67% (n=2041) had values between 15 and 29 (full distribution shown in **eFigure**).

Observation Time and Deaths

Crude death rates were highest in hemodialysis and lowest in transplanted patients (**Table 2; Figure 1**). When stratified by age, crude mortality rates were considerably lower in CKD compared to dialysis patients, but remained higher than in transplanted patients (**Figure 2**).

Risk of Dialysis and Death in CKD

In CKD patients, both the analysis of time to death and time to dialysis were affected by the concurrent risk of starting dialysis or dying, respectively: older age was associated with an increased risk of death, but a decreased risk of dialysis progression (**Table 3**). When analysing death and dialysis as a composite outcome, age displayed a borderline association. Having an eGFR of <15 compared to 15-29 at inclusion was associated with an almost 3-fold increased risk of death or dialysis, while male sex was associated with a smaller risk increase, as was low compared to high education, and presence of comorbidity.

Mortality Compared to the General Population

Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.3-4.0) for CKD, 5.6 (95%CI 3.5-8.9) for transplanted, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis patients (**Figure 3**). Mortality hazard ratios were statistically significant for cardiovascular as well as non-cardiovascular deaths for all groups.

Mortality in Chronic Kidney Disease versus Renal Replacement Therapy

In a direct comparison of patients in different health states (conditioned on age, sex, diabetes status, education level, and index year), all groups differed significantly from each other in terms of mortality hazard: transplanted patients had the lowest risk, followed by patients with CKD stages 4 and 5,

peritoneal dialysis, and hemodialysis patients (**Table 4**; all P<.001). Compared to chronic kidney disease patients, peritoneal dialysis had a 1.7 (95%CI 1.4-2.1) and hemodialysis patients a 2.6 (95%CI 2.3-2.9) times greater mortality hazard.

Education Level and Mortality

Less than 9 years compared to more than 12 years of education was associated with an increased mortality hazard overall (hazard ratio 1.4, 95%CI 1.2-1.7; **Figure 4**). The hazard ratio point estimate was elevated in all health states, but did not reach statistical significance in the smaller peritoneal dialysis and transplanted groups.

DISCUSSION

Principal Findings

In this population-based cohort study relative age-adjusted mortality was lowest in the transplanted group followed by CKD, peritoneal dialysis, and hemodialysis. Compared to dialysis patients, CKD patients had lower absolute mortality in age-adjusted analyses, lower relative mortality versus the general population, and lower relative mortality in direct comparison with dialysis patients. We did not find support for mortality in CKD to be similar to dialysis mortality.

Strengths & Weaknesses

This study was population-based, and data were collected in routine clinical care to which there is universal access in Sweden. No restrictions were set regarding demography or comorbidities, increasing generalizability. Another strength was that we followed patients from CKD to death directly, or via different forms of renal replacement therapy. We could estimate death rates in CKD stages 4 and 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same calendar period and at the same hospitals.

Using the unique personal identity number of each Swedish resident and linkage to national mortality data, follow-up was complete. Using national registers, we could also collect data on comorbidities, as well as match general population controls to each patient, which is likely to result in more accurate estimates than if using aggregated life-table data.

One limitation was that while all renal replacement therapy patients in Stockholm County were included, an unknown number of CKD patients were missed: CKD is under-diagnosed and many patients are identified only at acute dialysis start, or die before identification. The latter may have led to underestimation of mortality in CKD stage 4 and 5 population. Our results should therefore only be generalized to CKD patients in nephrology care.

Secondly, comparing mortality estimates in the respective health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the CKD health state.[16] However, such channeling of survivors would likely decrease the mortality differential between CKD and dialysis patients, indicating that our estimates of excess mortality in dialysis versus CKD may be conservative. To be selected for transplantation several prognostic factors are also considered, such as age and diabetes (which we adjusted for), but also general frailty (which we did not capture beyond certain comorbidities). Also, the lower mortality in peritoneal dialysis compared to hemodialysis should be interpreted with caution, as patients may transfer to hemodialysis at the end of life, inflating hemodialysis mortality estimates. However, some observations could support our finding of lower mortality in peritoneal dialysis than hemodialysis: data indicate that more frequent dialysis is beneficial,[17] and peritoneal dialysis does not seem to result in the same degree of myocardial stunning,[5] two factors that could contribute to lower mortality rates in peritoneal dialysis.

Finally, several important potential confounders were taken into account, such as age, sex, diabetes status, and education level, but residual confounding due to other risk factors cannot be ruled out.

Previous Research

Go et al[1] analysed 8458 insured CKD stage 4 and 5 patients with similar mean age as in our study, and similar prevalence of diabetes. Their sample was predominantly female compared to only 35% women in our study. They found age-standardised death rates of 11 and 14 per 100 person-years in

CKD stage 4 and 5, respectively, approaching the levels seen in dialysis. The death rates were standardised to their full study population which was comparatively young (mean age 52 years), complicating comparisons of absolute mortality rates with our study (mean age 66 years). They reported adjusted mortality hazard ratios of 3.2 and 5.9 for the two groups versus insured patients with eGFR≥60.

In a meta-analysis of more than 100,000 patients, Matsushita et al[4] used eGFR 90-104 as reference and found mortality hazard ratios for CKD stage 4 patients between 4 and 7 over a range of urine albumin-to-creatinine ratios. Our findings for CKD stage 4 and 5, versus matched general population controls, seem largely congruent with both these previous studies, but appear lower than the standardised mortality ratio of 8.3 reported by Evans et al from Sweden.[2] This discrepancy is most likely explained by their exclusion of patients ≥75 years old (a patient segment making up 33% of our sample in the current study), as relative mortality compared to the general population decreases with age, pushing our estimates downwards compared to Evans et al's.

Regarding dialysis mortality, we found both cardiovascular and non-cardiovascular mortality to be elevated, similar to findings from a large European analysis of dialysis mortality by de Jager et al.[3] They analysed all dialysis patients as a group, while we separated peritoneal dialysis and hemodialysis patients (for which we found differential mortality).

We also found an association between education level and CKD progression, as well as survival in renal replacement therapy. This is in agreement with Swedish findings regarding risk factors for chronic renal failure (unskilled workers versus professionals),[18] and a Danish study on risk of renal replacement therapy (low versus high income families, and low versus high education level).[19]

Implications

As mortality increases after both peritoneal and hemodialysis initiation, optimal timing of dialysis start has been debated, particularly as dialysis is initiated at higher eGFR today than previously: in the United States in 1996 only 4% started dialysis with eGFR>15, while 15% did in 2005.[20] The trend has been similar in Europe.[21] A recent randomized controlled trial gave no indication that early start was beneficial for survival.[22] Our data showing much higher mortality in both peritoneal dialysis and hemodialysis compared to CKD patients, together with previous findings, indicate that caution should be exercised before initiating dialysis.

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Competing interest statement
JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors
MN, SHJ, CGE, and BH conceived the study hypothesis. MN and JE conducted the statistical analyses. MN wrote the first draft of the manuscript. MN, SHJ, JE, CGE, and BH critically reviewed and contributed to the final draft. All authors are guarantors.

Ethical approval
Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden (DNR: 2009/1225-31/5).

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BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

Data sharing statement
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Table 1 Participant characteristics at chronic kidney disease register inclusion, start of dialysis or transplantation[a]

	Chronic Kidney Disease			Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
	Stage 4	Stage 5	Stages 4 & 5			
N	2041	999	3040	725	1791	606
Sex (% men)	1389 (68%)	586 (59%)	1975 (65%)	461 (64%)	1130 (63%)	387 (64%)
Age (Years)						
Mean (SD)	67 (15)	65 (15)	66 (15)	60 (15)	62 (15)	48 (12)
Median (25^{th}-75^{th})	70 (58-78)	68 (56-77)	69 (58-78)	62 (51-72)	65 (54-75)	50 (39-58)
n (%)						
18-49y	288 (14%)	164 (16%)	452 (15%)	165 (23%)	353 (20%)	310 (51%)
50-59y	289 (14%)	158 (16%)	447 (15%)	169 (23%)	324 (18%)	187 (31%)
60-69y	457 (22%)	217 (22%)	674 (22%)	187 (26%)	446 (25%)	107 (18%)
≥70y	1007 (49%)	460 (46%)	1467 (48%)	204 (28%)	668 (37%)	2 (0%)
Education[b]						
≤9y	370 (28%)	211 (30%)	581 (29%)	153 (26%)	414 (31%)	127 (21%)
10-12y	565 (42%)	276 (40%)	841 (41%)	240 (40%)	546 (41%)	255 (42%)
>12y	361 (27%)	162 (23%)	523 (26%)	177 (30%)	275 (20%)	212 (35%)
Missing	35 (3%)	49 (7%)	84 (4%)	26 (4%)	112 (8%)	12 (2%)
Comorbidity[c]						
Diabetes	778 (38%)	311 (31%)	1 089 (36%)	229 (32%)	634 (35%)	134 (22%)
Malignancies	355 (17%)	156 (16%)	511 (17%)	91 (13%)	319 (18%)	29 (5%)
Circulatory Disease	1678 (82%)	739 (74%)	2417 (80%)	598 (82%)	1484 (83%)	461 (76%)
Hypertension	1391 (68%)	613 (61%)	2004 (66%)	517 (71%)	1193 (67%)	402 (66%)
Cardiovascular Disease	946 (46%)	379 (38%)	1325 (44%)	297 (41%)	867 (48%)	147 (24%)
Myocardial Infarction[d]	276 (14%)	117 (12%)	393 (13%)	93 (13%)	236 (13%)	21 (3%)
Stroke	228 (11%)	117 (12%)	345 (11%)	64 (9%)	185 (10%)	27 (4%)
COPD[e]	133 (7%)	55 (6%)	188 (6%)	32 (4%)	121 (7%)	11 (2%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or sub-diagnosis of the respective ICD-codes used (specified in **eTable 1**)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

Table 2 Mortality and accumulated person-years by health state[a]

	Chronic Kidney Disease Stage 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
N	3040	725	1791	606
Person-Years	**6553**	**1113**	**3680**	**2935**
Mean (SD)	2.2 (1.7)	1.5 (1.4)	2.1 (2.2)	4.8 (3.2)
Median (25^{th}-75^{th} Percentile)	1.7 (0.8-3.2)	1.1 (0.5-2.3)	1.3 (0.4-3.0)	4.6 (2.1-7.4)
Deaths (1999-2010)	**766**	**186**	**924**	**53**
Circulatory Deaths (1999-2008)[b]	381 (76%)	128 (85%)	513 (69%)	26 (67%)
Deaths/1000 Person-Years (95%CI)				
Patients	117 (109-125)	167 (145-193)	251 (235-268)	18 (14-24)
Matched General Population Controls[c]	51 (48-54)	21 (17-26)	20 (18-22)	4 (3-5)

[a] SD=standard deviation

[b] Causes of death not available for deaths occurring in 2009 and 2010 (530/1929 deaths; 27%). Cardiovascular causes determined from main *and* contributory diagnoses.

[c] Matched 5:1 by age, sex, and index year

Table 3 Adjusted hazard ratios for risk of progressing to dialysis, death, and death or dialysis for chronic kidney disease 4 and 5 patients (conditioned on index year; n=3040)

	Adjusted Hazard Ratio (95%CI)		
	Dialysis	Death	Death or Dialysis
eGFR[a]<15	3.98 (3.47-4.56) P<.001	1.62 (1.37-1.92) P<.001	2.75 (2.48-3.04) P<.001
eGFR[a] 15-29 (reference)	1.0	1.0	1.0
Demography			
Male	1.13 (0.99-1.28) P=.06	1.15 (0.98-1.34) P=.08	1.14 (1.03-1.25) P=.01
Female (reference)	1.0	1.0	1.0
Age			
18-49y	1.29 (1.07-1.56) P=.009	0.31 (0.15-0.65) P=.002	1.19 (0.99-1.42) P=.06
50-59y (reference)	1.0	1.0	1.0
60-69y	0.98 (0.81-1.18) P=.84	2.36 (1.65-3.39) P<.001	1.16 (0.99-1.36) P=.07
≥70y	0.73 (0.60-0.88) P=.001	3.42 (2.43-4.80) P<.001	1.17 (1.00-1.37) P=.05
Education Level			
≤9y	1.12 (0.93-1.35) P=.2	1.43 (1.08-1.90) P=.01	1.21 (1.04-1.41) P=.01
10-12y	1.09 (0.92-1.30) P=.3	1.24 (0.93-1.64) P=.1	1.15 (0.99-1.33) P=.06
>12y (reference)	1.0	1.0	1.0
Comorbidity			
Diabetes	1.31 (1.15-1.49) P<.001	1.26 (1.08-1.46) P=.003	1.30 (1.18-1.43) P<.001
Circulatory Disease	1.15 (0.99-1.33) P=.06	1.59 (1.27-2.00) P<.001	1.23 (1.09-1.39) P=.001
Malignancy	1.03 (0.88-1.21) P=.69	1.50 (1.29-1.75) P<.001	1.24 (1.11-1.38) P<.001
Events	**1075**	**766**	**1841**
Person-Years[b]	**6553**	**6553**	**6553**

[a] Estimated glomerular filtration rate (using the MDRD formula; ml/min/1.73m^2)

[b] Patients censored at time of death, transition to another health state or end of follow-up, whichever came first. Failures in chronic kidney disease include only deaths occurring while patients are in the chronic kidney disease health state, not deaths occurring after switching to renal replacement therapy.

Table 4 Conditional[a] mortality hazard ratios for chronic kidney disease 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients compared to each other

	Mortality hazard ratios (95%CI)			
	Chronic kidney disease 4 & 5	Peritoneal dialysis	Hemo-dialysis	Transplantation
Chronic kidney disease stage 4 & 5	1.0	1.7 (1.4-2.1) P<.001	2.6 (2.3-2.9) P<.001	0.5 (0.3-0.7) P<.001
Peritoneal dialysis	0.6 (0.5-0.7) P<.001	1.0	1.5 (1.2-1.8) P<.001	0.3 (0.2-0.4) P<.001
Hemodialysis	0.4 (0.3-0.4) P<.001	0.7 (0.6-0.8) P<.001	1.0	0.2 (0.1-0.3) P<.001
Transplantation	2.1 (1.5-3.0) P<.001	3.6 (2.5-5.3) P<.001	5.3 (3.7-7.6) P<.001	1.0
N	**3040**	**725**	**1791**	**606**
Deaths	**766**	**186**	**924**	**53**
Person-Years	**6553**	**1113**	**3680**	**2935**

[a] Models conditioned on age (18-49y, 50-59y, 60-69y, ≥70y), sex, education level (≤9y, 10-12y, >12y), diabetes, and index year

FIGURE LEGENDS

Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis and transplanted patients, as well as matched general population controls

Figure 2 Crude mortality rates by health state and age

Figure 3 Conditional all cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls

Figure 4 Mortality hazard ratios by education level using >12 years of education as reference

FIGURES

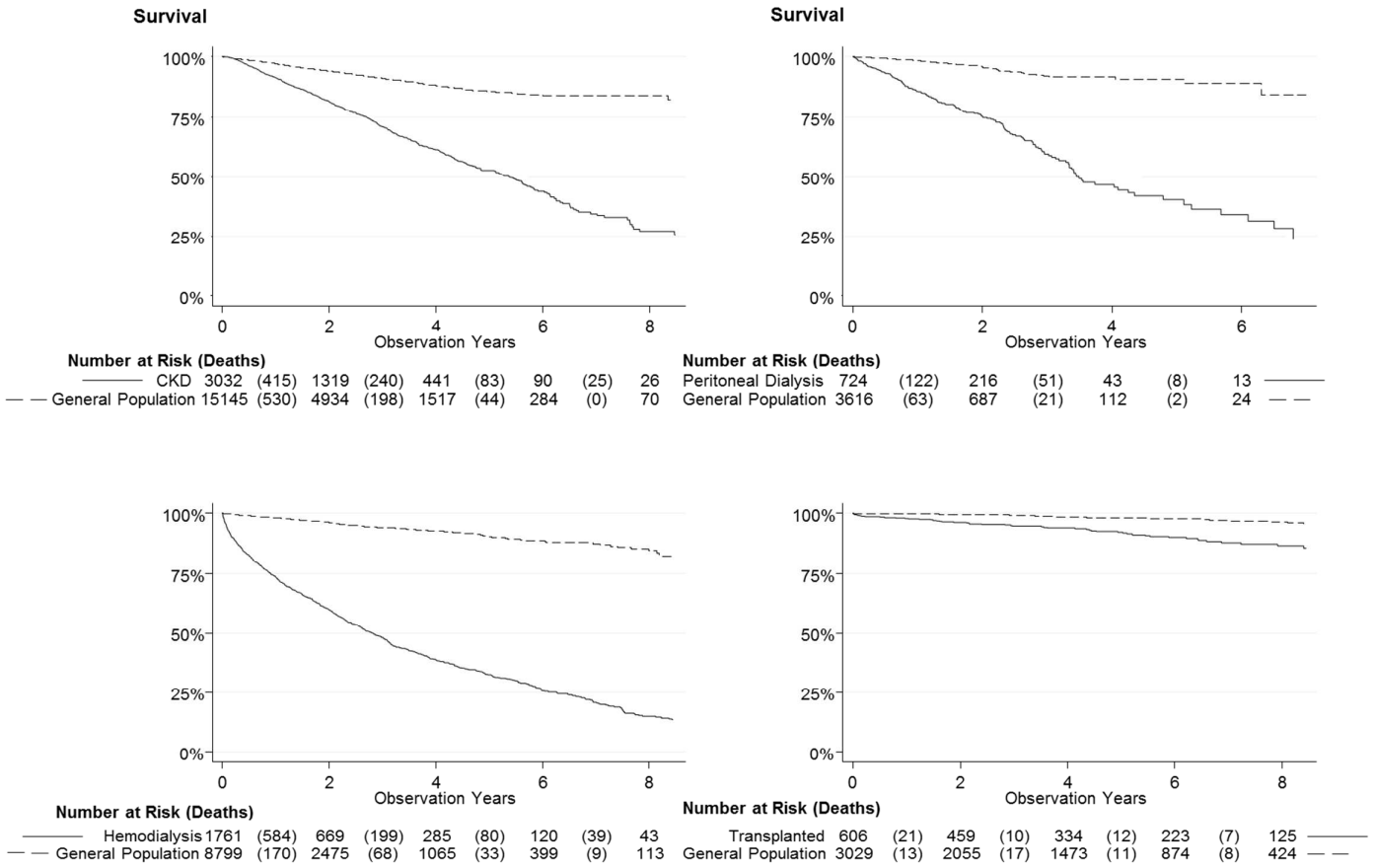


Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis, and transplanted patients, as well as matched general population controls[ab]

[a] Patients followed until death, health-state transition, emigration, or end of follow-up, whichever came first. Controls matched 5:1 by age, sex, and index year

[b] Numbers within parentheses represent deaths

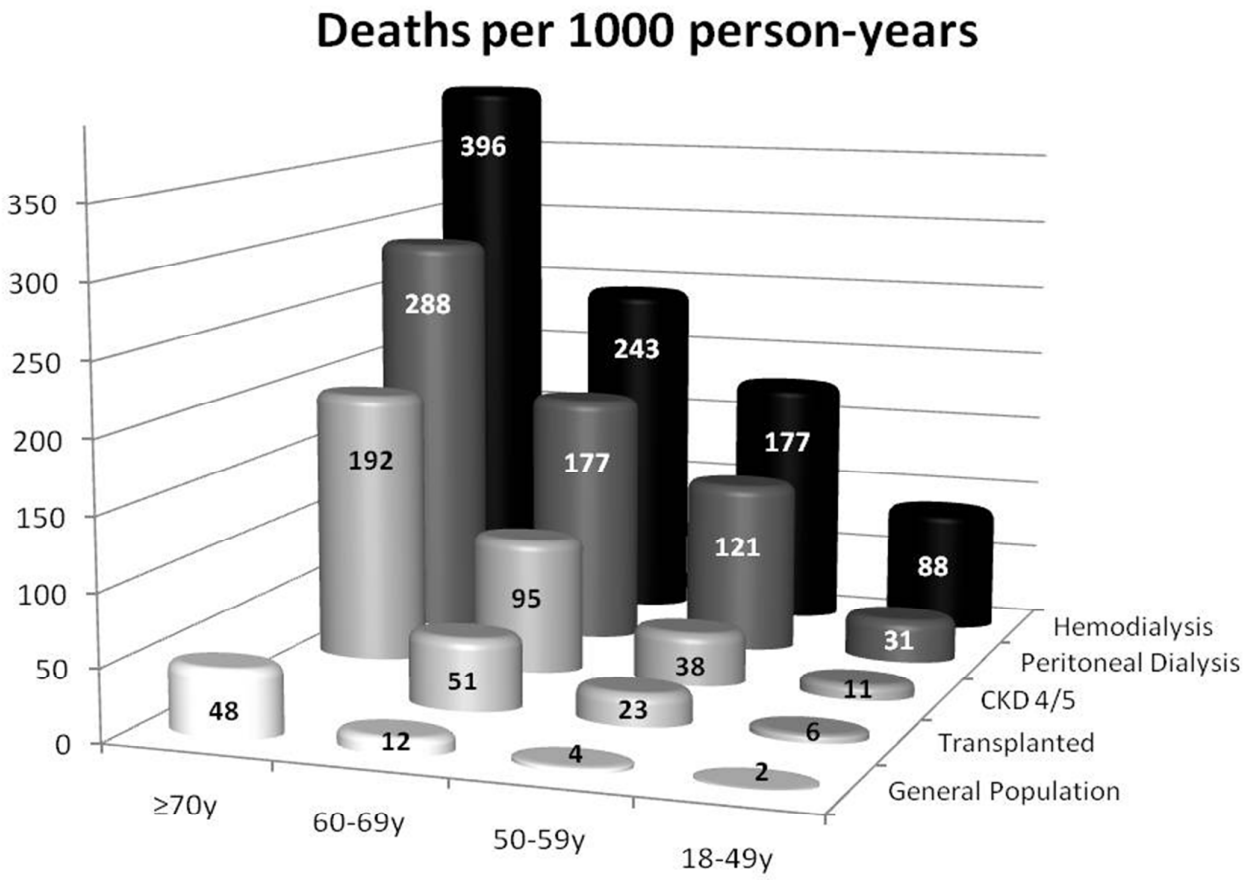


Figure 2 Crude mortality rates by health state and age[ab]

[a] General population=matched by age, sex, and index year(to the full cohort)
CKD 4/5=Chronic kidney disease stages 4 or 5
[b] Person-years, deaths and confidence intervals provided in **eTable 3**

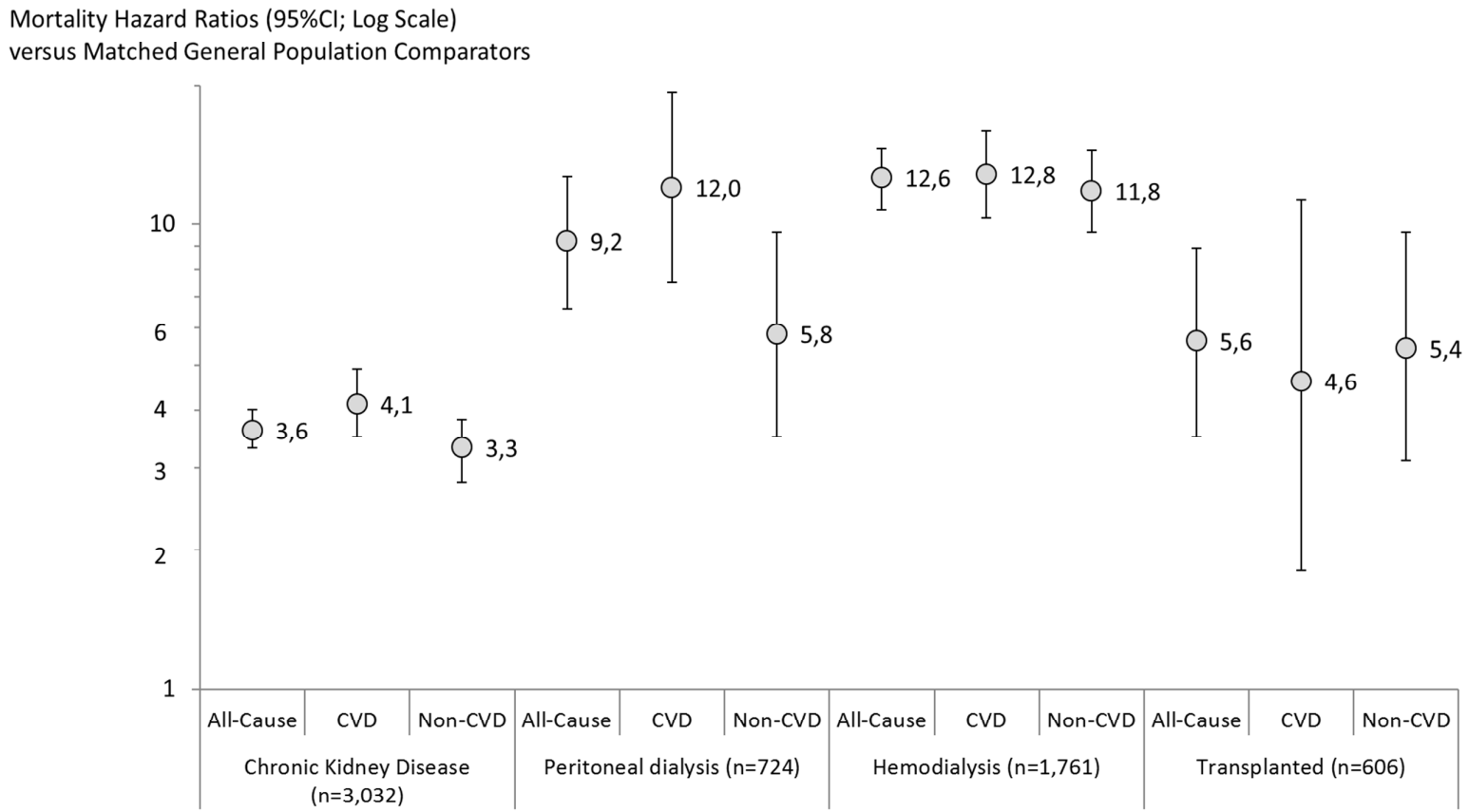


Figure 3 All cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls[a]

[a] General population controls matched 5:1 by age, sex, and index year. Models conditioned on age category (18-49y, 50-59y, 60-69y, ≥70y), sex, education level (≤9y, 10-12y, >12y), diabetes, and index year. Underlying data shown in **eTable 4**.

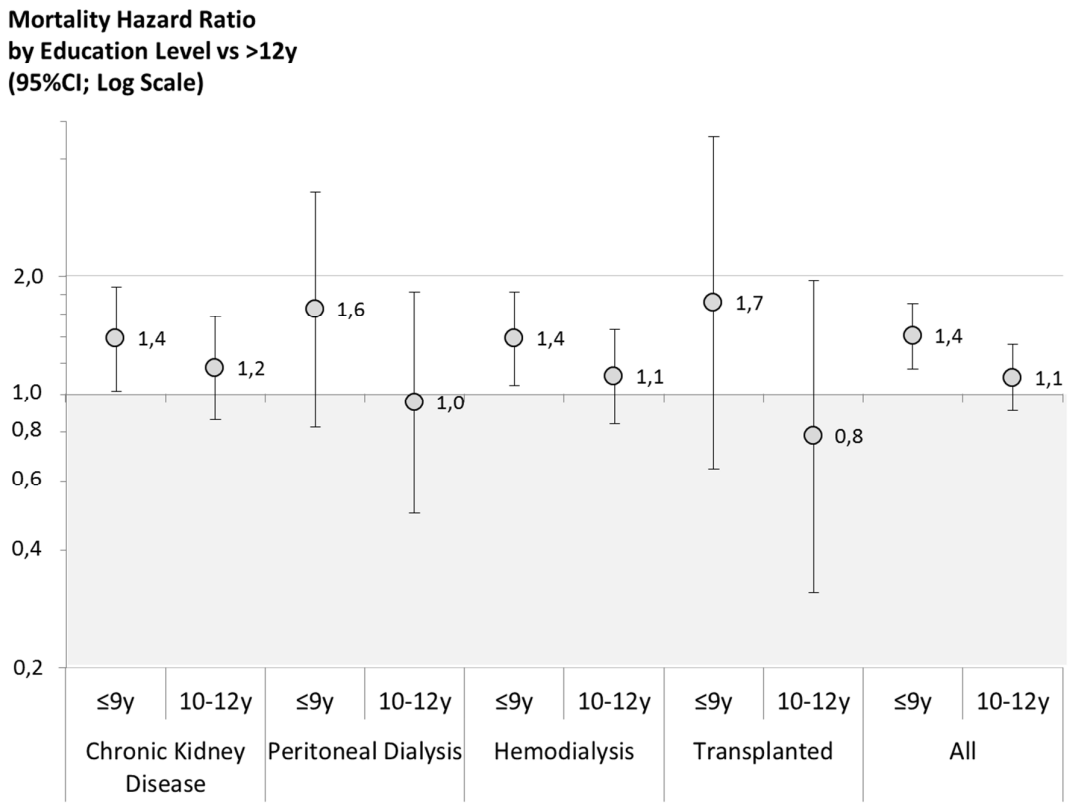


Figure 4 Mortality hazard ratios by education level using >12 years of education as reference[a]

[a] Models conditioned on age category, sex, diabetes status, and index year; Data on education level only available for patients <75y, explaining the reduced sample sizes.

Supplementary Web Appendix

Mortality in Chronic Kidney Disease & Renal Replacement Therapy:
A Population-Based Cohort Study

Martin Neovius (associate professor), Stefan H Jacobson (senior nephrologist, professor), Jonas Eriksson (doctoral student), Carl-Gustaf Elinder (senior nephrologist, professor) & Britta Hylander (senior nephrologist, associate professor)[4]

eTable 1 International Classification of Diseases (ICD) codes for comorbidities[a] and causes of death[b]

	ICD 10	ICD 9
Diabetes	E10-E11	250
Malignancies	C00-C99	140-208
Circulatory	I00-I99	390-459
Hypertension	I10-I15	401-405
Cardiovascular Disease	I20-I51	410-429
Myocardial Infarction	I21	410
Stroke	I60-I64	430-438
Lower-Extremity Deep Vein Thrombosis	I26, I80-I82	451-453, 415B
Chronic Obstructive Pulmonary Disease	J41-J44	490-492, 496
Uremia	N00-N19	580-599

[a] Comorbidities assessed from 10 years prior to the index year until the index year (1989 to 2010), i.e. both ICD 9 and ICD 10 codes used

[b] Deaths occurring from inclusion to end of follow-up (1999-2010), i.e. only ICD 10 codes used

eTable 2 Characteristics of matched general population controls (matched by age, sex, and index year)

General Population Controls	Chronic Kidney Disease 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplanted
N	**15,145**	**3616**	**8799**	**3029**
Education[a]				
≤9y	2534 (25%)	673 (23%)	1640 (25%)	587 (19%)
10-12y	4171 (41%)	1263 (43%)	2713 (41%)	1266 (42%)
>12y	3173 (31%)	951 (32%)	2077 (31%)	1110 (37%)
Missing	225 (2%)	66 (2%)	195 (3%)	66 (2%)
Comorbidity				
Diabetes	1037 (7%)	165 (5%)	495 (6%)	78 (3%)
Malignancies	1648 (11%)	270 (7%)	695 (8%)	84 (3%)
Circulatory	4813 (32%)	828 (23%)	2217 (25%)	309 (10%)
Hypertension	2279 (15%)	371 (10%)	973 (11%)	129 (4%)
Cardiovascular Disease	2907 (19%)	459 (13%)	1336 (15%)	126 (4%)
Myocardial Infarction[b]	634 (4%)	109 (3%)	266 (3%)	22 (1%)
Stroke	810 (5%)	131 (4%)	375 (4%)	30 (1%)
COPD[c]	508 (3%)	65 (2%)	221 (3%)	17 (1%)

[a] Education only available in patients <75y
[b] Subgroup of cardiovascular disease
[c] Chronic obstructive pulmonary disease

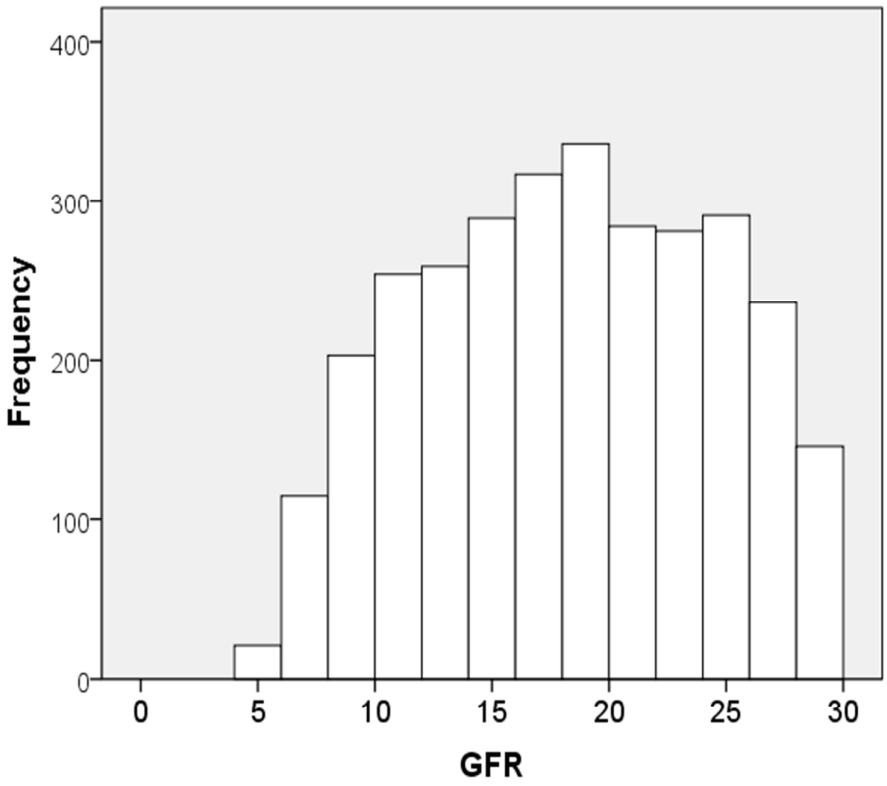
eTable 3 Underlying data for Figure 2

By Age	Chronic Kidney Disease4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplanted
N	**3040**	**725**	**1791**	**606**
Person-Years	**6553**	**1113**	**3680**	**2935**
18-49y	1002	227	725	1539
50-59y	1097	265	717	976
60-69y	1444	287	996	409
≥70y	3009	333	1240	9
Deaths (All Causes)	**766**	**186**	**924**	**53**
18-49y	9	7	64	10
50-59y	41	32	127	22
60-69y	137	51	242	21
≥70y	579	96	491	-
Deaths/100 Person-Years (95%CI)	**11.7 (10.9-12.5)**	**16.7 (14.5-19.3)**	**25.1 (23.5-26.8)**	**1.8 (1.4-2.4)**
18-49y	0.9 (0.5-1.7)	3.1 (1.5-6.5)	8.8 (6.9-11.3)	0.6 (0.3-1.2)
50-59y	3.7 (2.8-5.1)	12.1 (8.5-17.1)	17.7 (14.9-21.1)	2.3 (1.5-3.4)
60-69y	9.5 (8.0-11.2)	17.7 (13.5-23.3)	24.3 (21.4-27.6)	5.1 (3.3-7.9)
≥70y	19.2 (17.7-20.9)	28.8 (23.6-35.2)	39.6 (36.2-43.2)	-

eTable 4 Underlying data for Figure 3: Conditional[a] mortality hazard ratios for chronic kidney disease 4 and 5, peritoneal dialysis, hemodialysis and transplanted patients compared to matched general population controls

Patients vs Matched General Population Controls	Mortality Hazard Ratio (95%CI)			
	Chronic Kidney Disease 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplantation
All Cause	3.6 (3.2-4.0) P<.001	9.2 (6.6-12.7) P<.001	12.6 (10.8-14.6) P<.001	5.6 (3.5-8.9) P<.001
Cardiovascular Disease	4.1 (3.4-4.9) P<.001	12.0 (7.5-19.3) P<.001	12.8 (10.3-15.9) P<.001	4.6 (1.8-11.3) P=.001
Non-Cardiovascular Disease	3.2 (2.8-3.8) P<.001	5.8 (3.5-9.6) P<.001	11. 8 (9.6-14.5) P<.001	5.4 (3.1-9.6) P<.001
N				
Patients	3032	724	1761	606
Controls	15,145	3616	8799	3029
Deaths (All Cause)				
Patients	766	186	919	53
Controls	774	87	285	53
Person-Years				
Patients	6542	1109	3607	2936
Controls	25,652	4115	14,318	12,828
Data for patients and controls 1999-2008 (i.e. individuals with information on cause-specific mortality)				
N				
Patients	2482	627	1531	522
Controls	11,063	2909	7151	2319
Deaths (All Cause)				
Patients	707	170	871	50
Controls	670	75	266	51
Person-Years				
Patients	6164	1056	3441	2868
Controls	22,765	3693	13,160	12,137

[a]Models stratified by age, sex, education, diabetes, and index year (general population controls matched 5:1 by age, sex, and index year)



eFigure Distribution of estimated glomerular filtration rate (GFR; ml/min/1.73m^2) in patients with chronic kidney disease stage 4 and 5[a]

[a] Estimated using the MDRD formula

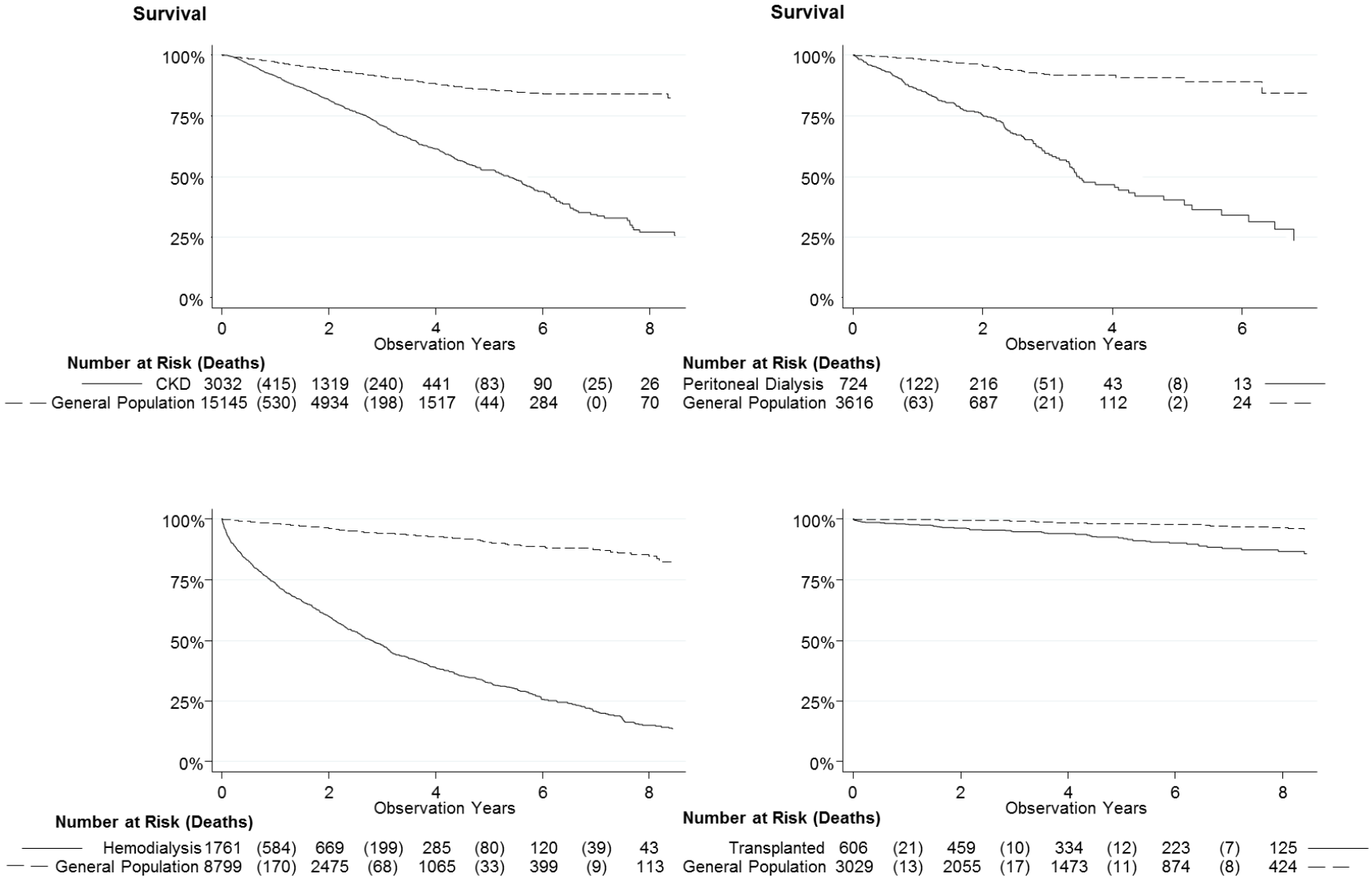


Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis, and transplanted patients, as well as matched general population controls

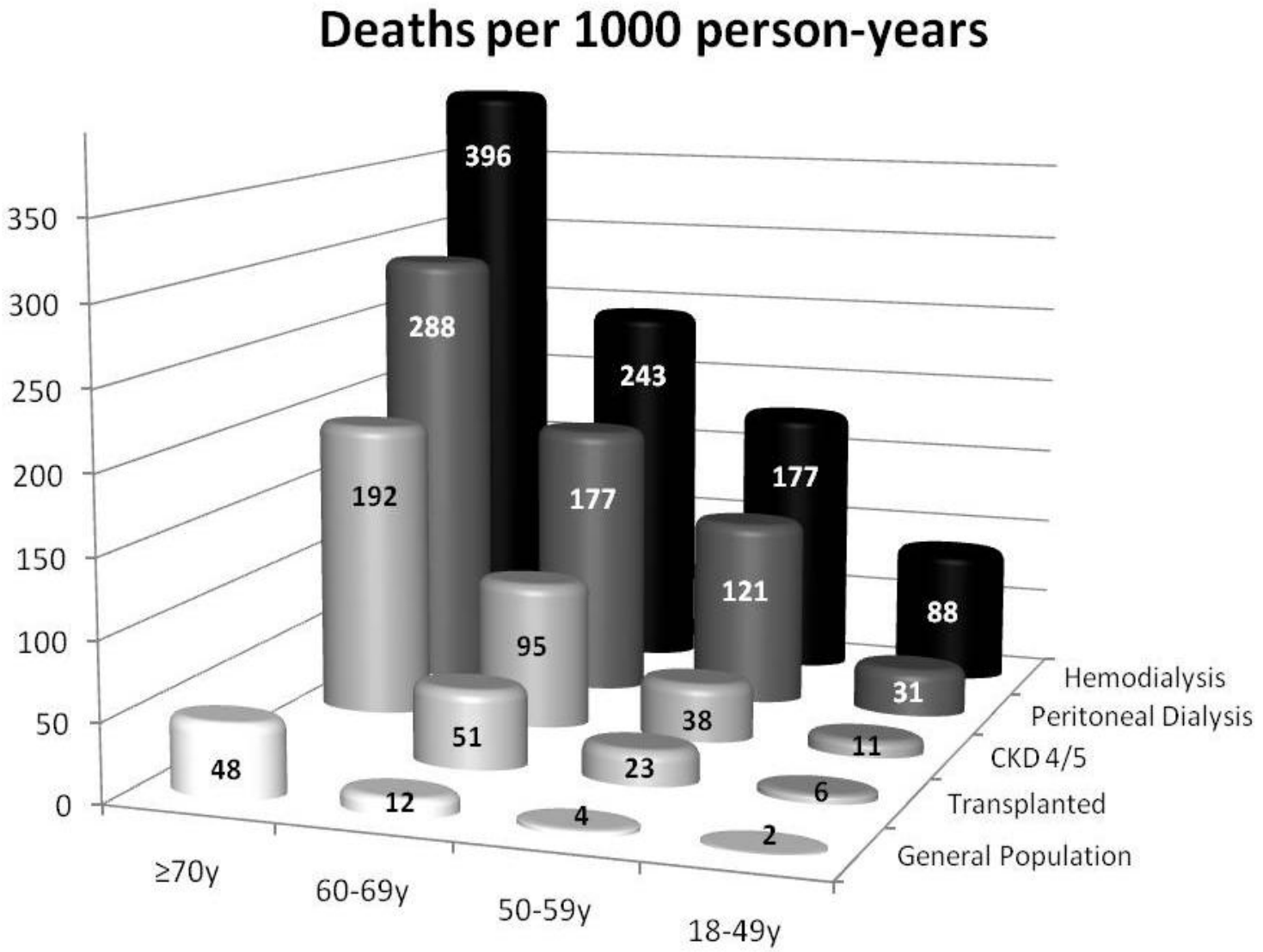


Figure 2 Crude mortality rates by health state and age

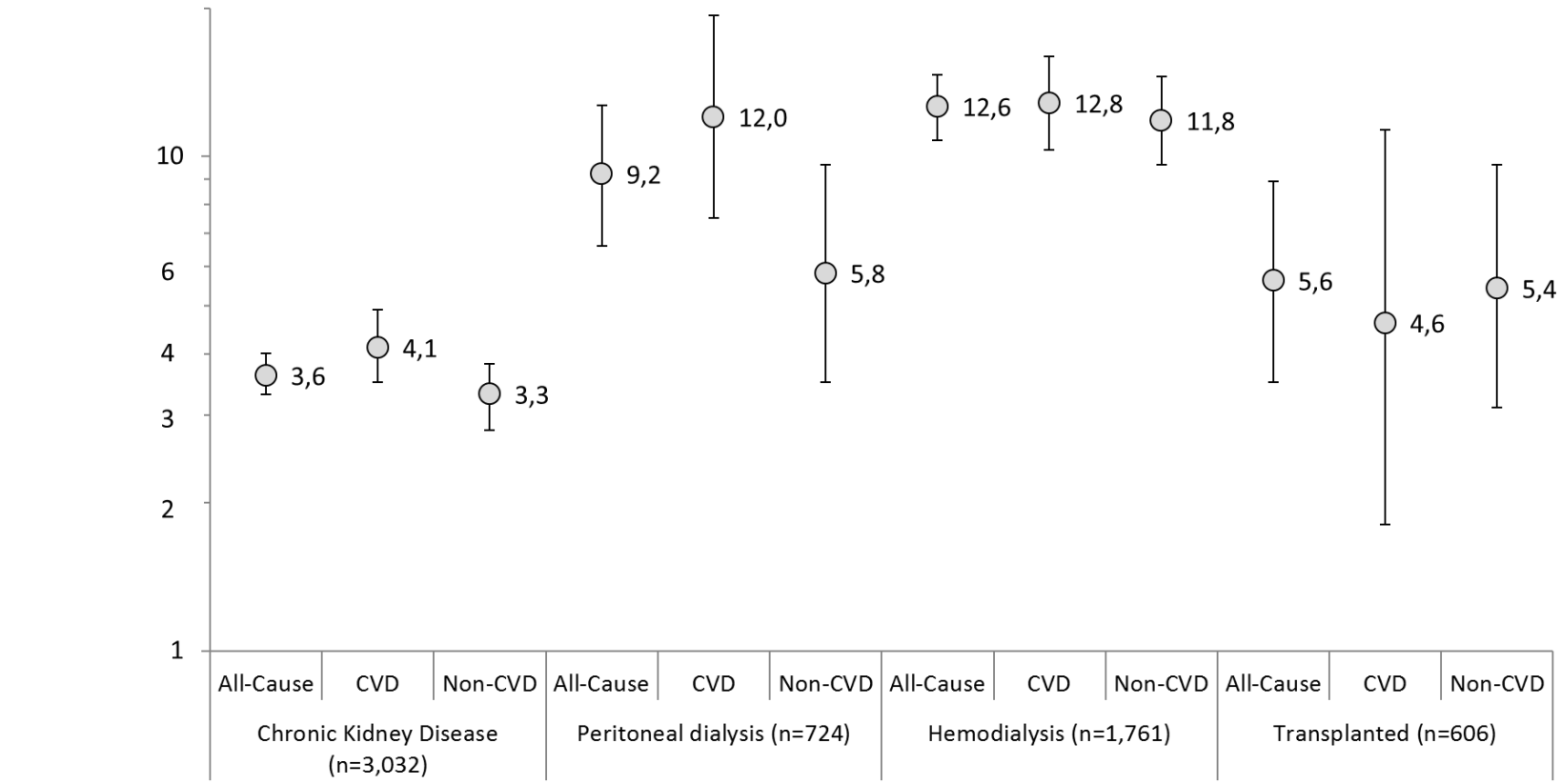


Figure 3 All cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls

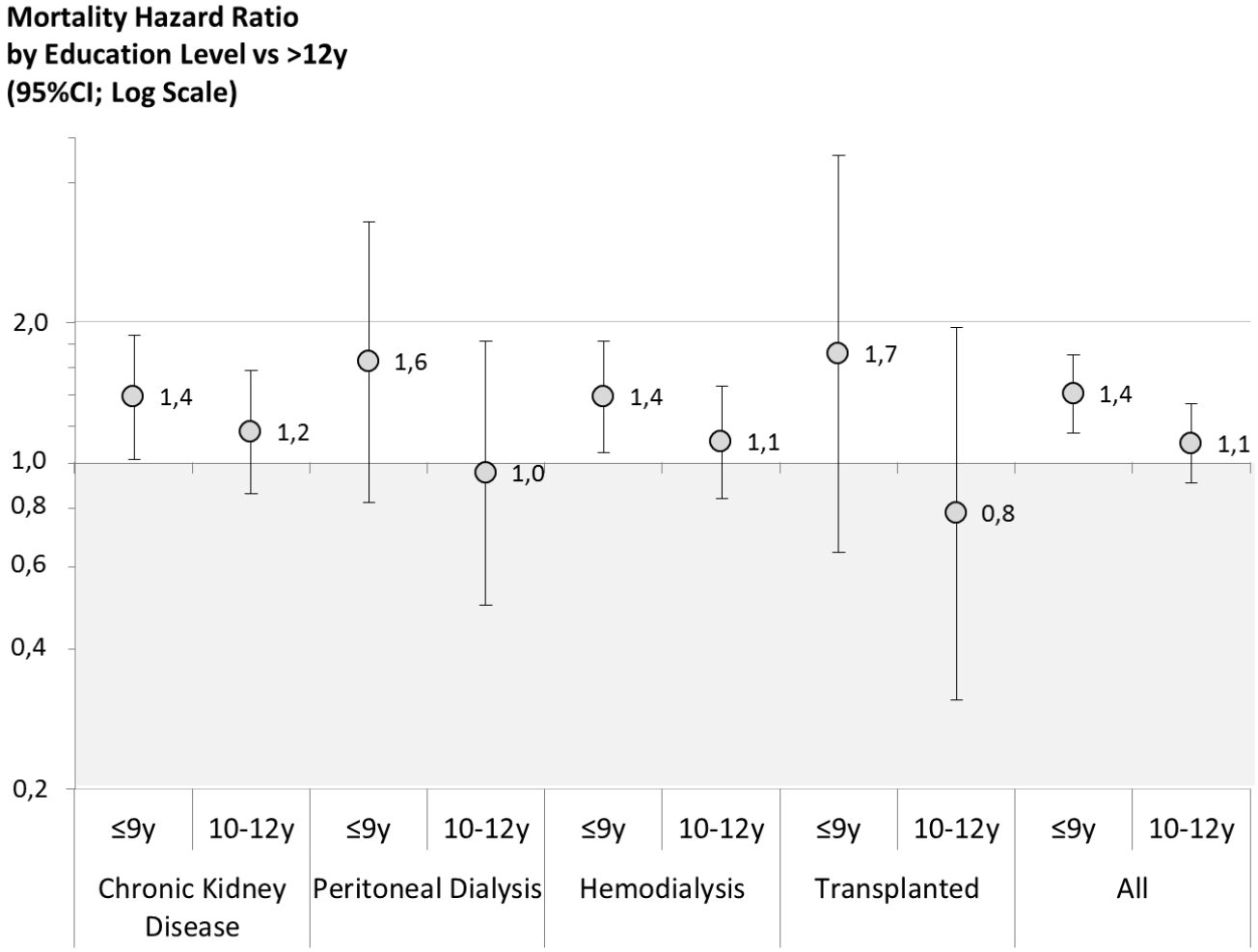


Figure 4 Mortality hazard ratios by education level using >12 years of education as reference

Recommended Format for the Reporting of Observational Cohort Studies According to the STROBE Group

Section	Item	Recommendation	Page
Title & Abstract	1	Indicate the study's design with a commonly used term in the title or the abstract.	1
		Provide in the abstract an informative and balanced summary of what was done and what was found.	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported.	4
Objectives	3	State specific objectives, including any prespecified hypotheses.	4
Methods			
Study design	4	Present key elements of study design early in the paper.	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection.	5-6
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow up.	5
		For matched studies, give matching criteria and number of exposed and unexposed.	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than 1 group.	5-6
Bias	9	Describe any efforts to address potential sources of bias.	5-6
Study size	10	Explain how the study size was arrived at.	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	6
Statistical methods	12	Describe all statistical methods, including those used to control for confounding.	6
		Describe any methods used to examine subgroups and interactions.	
		Explain how missing data were addressed.	
		If applicable, explain how loss to follow up was addressed.	
		Describe any sensitivity analyses.	
Results			
Participants	13*	Report numbers of individuals at each stage of study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analyzed.	7
		Give reasons for nonparticipation at each stage.	
		Consider use of a flow diagram.	
Descriptive data	14*	Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders.	7, 14
		Indicate number of participants with missing data for each variable of interest.	
		Summarize follow up time (eg, average and total amount).	
Outcome data	15*	Report numbers of outcome events or summary measures over time.	7-8 15-17
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included.	8
		Report category boundaries when continuous variables were categorized.	16-17
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	8
Discussion			
Key results	18	Summarize key results with reference to study objectives.	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalizability	21	Discuss the generalizability (external validity) of the study results.	9
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	11

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Mortality in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

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Keywords:	chronic kidney disease, Dialysis < NEPHROLOGY, mortality, renal replacement therapy, transplantation

Mortality in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

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Short Title (max 45 characters): Chronic kidney disease and mortality

Word count, Tables & Figures

Word Count:	2778 words (excl abstract; max 4000)
Abstract Word Count:	300 words (max 300)
Tables:	3
Figures:	4
eTables:	4
eFigures:	1

Key words: chronic kidney disease, dialysis, mortality, renal replacement therapy, transplantation

ABSTRACT (300 words)

Objective: To compare mortality in chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min/1.73m^2), peritoneal dialysis, hemodialysis, and transplanted patients.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Swedish adult patients with chronic kidney disease stage 4 or 5 (n=3040; mean age 66y), peritoneal dialysis (n=725; 60y), hemodialysis (n=1791; 62y), and renal transplantation (n=606; 48y) were identified in Stockholm County clinical quality registers for renal disease between 1999 and 2010. Five general population controls were matched to each patient by age, sex, and index year.

Exposure: Chronic kidney disease status (stage 4 or 5/peritoneal dialysis/hemodialysis/ transplanted)

Primary Outcome: All cause mortality ascertained from the Swedish Causes of Death Register. Mortality hazard ratios were estimated using Cox regression conditioned on age, sex, diabetes status, education level, and index year.

Results: During 6553 person-years 766 patients with chronic kidney disease stage 4 or 5 died (deaths/100 person-years 12, 95%CI 11-13) compared with 186 deaths during 1113 person-years in peritoneal dialysis (17, 95%CI 15-19), 924 deaths during 3680 person-years in hemodialysis (25, 95%CI 23-27), and 53 deaths during 2935 person-years in transplanted patients (1.8, 95%CI 1.4-2.4). Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.2-4.0) for chronic kidney disease, 5.6 (95%CI 3.5-8.9) for transplanted patients, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis. In direct comparison versus chronic kidney disease, the mortality hazard ratio was 1.7 (95%CI 1.4-2.1) for peritoneal dialysis, 2.6 (95%CI 2.3-2.9) for hemodialysis, and 0.5 (95%CI 0.3-0.7) for transplanted patients.

Conclusion: We did not find support for mortality in CKD to be similar to dialysis mortality. Patients with chronic kidney disease stage 4 or 5 had considerably lower mortality risk than dialysis patients, and considerably higher risk than transplanted patients and matched general population controls.

ARTICLE FOCUS

- Chronic kidney disease and renal replacement therapy are associated with increased mortality
- Some studies suggest mortality in chronic kidney disease stage 4 and 5 to approach dialysis mortality rates
- No studies have compared mortality in chronic kidney disease, in different forms of dialysis, and after transplantation with the general population, and directly with each other

KEY MESSAGES

- Relative mortality risk versus matched general population controls was 4 in chronic kidney disease, 6 in transplanted patients, 9 in peritoneal dialysis and 13 in hemodialysis patients
- In direct comparison versus chronic kidney disease patients, relative mortality risk was 0.5 in transplanted patients, 1.7 in peritoneal dialysis, and 2.6 in hemodialysis
- The markedly increased mortality observed in both peritoneal dialysis and hemodialysis suggests that such therapies should not be started too early

STRENGTHS & LIMITATIONS

- This study was population-based with no restrictions regarding age or comorbidities, and data were collected in routine clinical care to which there is universal access in Sweden
- Using the unique personal identity number of each Swedish resident, follow-up was complete regarding mortality
- Although all renal replacement therapy patients in the catchment area were included, an unknown number of chronic kidney disease stage 4 and 5 patients were missed, as the condition is underdiagnosed
- Direct comparison of mortality across different health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the chronic kidney disease health state

INTRODUCTION

Mortality is substantially elevated in chronic kidney disease (CKD) and dialysis patients,[1-3] with some studies describing CKD patients in stages 4 and 5 (estimated glomerular filtration rate [eGFR] 15-29 and <15 ml/min/1.73m^2, respectively) as having mortality rates approaching the rates in dialysis.[1] However, there are no studies directly quantifying the relative mortality in CKD, dialysis (separating peritoneal and hemodialysis), and transplanted patients.

An analysis of an insured US population found patients in CKD stages 4 and 5 to approach dialysis mortality rates with a 3- and 6-fold higher mortality risk, respectively, than patients with eGFR ≥60.[1] This can be compared with a standardised mortality ratio of 8 reported in Swedish incident CKD patients stages 4 and 5 followed for up to almost 7 years,[2] and with hazard ratios ranging from 3.7 to 7.0 for stage 4 patients (eGFR 15-29) with varying levels of albumin-to-creatinine-ratio in a meta-analysis of more than 100,000 patients, using patients with an eGFR of 90-104 as reference.[4]

Regarding dialysis mortality, a large European study showed an 8-fold higher age-standardised mortality due to both cardiovascular and non-cardiovascular death compared to the general population.[3] The study did not distinguish between peritoneal dialysis and hemodialysis.

These US and European studies indicate that mortality in CKD stages 4 and 5 may be as high as in dialysis. However, control groups differed between the studies (patients with normal kidney function defined as eGFR ≥60[1] or 90-104[4]; aggregated Swedish[2] or European life tables[3]), and mortality may differ between modes of dialysis.[5]

The aim of this population-based cohort study was to examine mortality in CKD stages 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients in relation to matched general population controls, and directly with each other.

METHODS

This population-based cohort study was performed in the Swedish health care system using patient data from clinical quality registers kept for quality of care evaluation in Stockholm County. These data sources were combined with matched general population controls, and enriched with outcome and exposure data via linkage to nationwide health registers kept by the National Board of Health & Welfare and demographic registers at Statistics Sweden. Register linkage was performed using the unique personal identity number assigned to each Swedish resident.[6] Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 9.4 million on December 31, 2010 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 2.1 million inhabitants, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, and patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient hospital care.[7] Care for CKD patients was a mix of mainly outpatient hospital and primary care. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[8] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[9] and the corresponding European guidelines.[10]

Quality Register Sources

CKD Patients: Data from the Stockholm County CKD Register were used, including adult CKD patients in stages 4 and 5 not on dialysis registered at Karolinska and Danderyd University Hospital from 1999 to 2010 in the outpatient setting. This does not include all CKD stage 4 and 5 patients in the county, as some get care elsewhere and some remain undetected. Stages 4 and 5 were defined as an eGFR of 15-29 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[11] Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed.

Renal Replacement Therapy Patients: Data on dialysis initiation, type of dialysis, and transplantation were collected from the Swedish Register of Renal Replacement Therapy, including all adult patients on renal replacement therapy in Stockholm County.[12 13]

The National Patient Register

Data on inpatient and outpatient hospital care were retrieved from the Swedish National Patient Register.[14] This register contains the personal identity number, visit/admission date (and discharge date for inpatients), and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10). The register reached national coverage in 1987 for inpatient care, and the outpatient component was added in 2001.

From inpatient and outpatient care registered in the National Patient Register, data on hospital visits listing diabetes, malignancies, circulatory disease, and chronic obstructive pulmonary disease were gathered. Visits listing these diagnoses were searched for during the last ten years (ICD-9 and ICD-10 codes provided in **eTable 1**).

Matched General Population Control Cohort

From the Register of the Total Population at Statistics Sweden, up to five general population controls were matched to each patient at the time of inclusion into the CKD register, and renal replacement therapy initiation, using age (+/-1 year), sex, and index year as matching factors. Data on emigration status and highest attained education were also retrieved from Statistics Sweden.

Outcome and Follow-Up

The primary outcome was all cause mortality. Secondary outcomes for CKD patients included initiation of renal replacement therapy and the composite outcome death or dialysis.

Dates and causes of death were retrieved from the Causes of Death Register kept by the National Board of Health and Welfare. Dates of death were available until July 31, 2010, while main and contributory death causes were available until December 31, 2008.

CKD and renal replacement therapy patients included from January 1, 1999, were analysed. Follow-up started at date of inclusion into the Stockholm CKD Register, dialysis initiation, or transplantation. Patients accrued person-time in a specific health state until death, transition to another health state, emigration, or July 31, 2010, whichever came first.

Statistical Analysis

Unadjusted incidence rates and Kaplan-Meier curves were used to present absolute risks. For CKD patients, a Cox proportional hazards model was used to model time to dialysis, and the composite outcome death or dialysis. The models were adjusted for age, sex, education level (≤9, 10-12, >12 years, missing), baseline eGFR (stage 4 versus 5), and comorbidity status, and index year.

Comparison versus the General Population: In mortality analyses versus matched general population controls, Cox models conditioned on age, sex, education level, diabetes status, and index year were used. Some patients did not have a full five controls, but were still included in the analyses, while patients with no controls were excluded. For dialysis and transplanted patients the Andersen-Gill[15] method was applied allowing for patients to re-enter a health state after exiting.

In order to investigate whether potential differences in all-cause mortality were driven by cardiovascular mortality, sensitivity analyses were performed for cardiovascular as well as non-cardiovascular deaths. An analysis was also performed to compare mortality by education level.

Direct Comparison of CKD versus Renal Replacement Therapy: To directly compare mortality in the different health states, a Cox model conditioned on age, sex, education level, diabetes status, and index year was used with health state as primary predictor.

Missing data on education level were handled using the missing indicator method. Data were complete on age, sex, and register-determined comorbidity status. Missing baseline eGFR resulted in exclusion from CKD analyses.

Statistical analyses were performed using SAS (version 9.3) and Stata (version 11). All P-values are two-sided and P-values <.05 were considered statistically significant.

RESULTS

A total of 4249 patients were included. Follow-up of mortality was complete and all patients were analysed, except for 19 CKD patients who were excluded due to missing baseline eGFR.

Patient characteristics at inclusion, dialysis initiation and transplantation are shown in **Table 1**. CKD patients were on average 66 years old at inclusion, while dialysis patients were younger, and transplanted patients much younger: 48% of CKD patients were more than 70 years old, compared to 37% of hemodialysis, 28% of peritoneal dialysis, and 0% of the transplanted patients. All groups were predominantly male, and the education level was broadly similar to that in the general population.

Regarding selected register-identified comorbidities, the CKD and dialysis patients were similar, while the younger transplanted group displayed much lower prevalence. More than 30% of patients (except the transplanted group) had diabetes, compared to 3-7% in the matched general population (**eTable 2**). Approximately 80% of patients had circulatory disease history at inclusion, with about 10% having had myocardial infarction and 10% stroke (except transplanted patients). In CKD and dialysis patients malignancies were also more common than in the general population.

In the CKD cohort at inclusion, the mean eGFR was 18 (SD 6; median 18; range 4.1-29.9). A third (n=999) had values <15, while 67% (n=2041) had values between 15 and 29 (full distribution shown in **eFigure**).

Observation Time and Deaths

Crude death rates were highest in hemodialysis and lowest in transplanted patients (**Table 2; Figure 1**). When stratified by age, crude mortality rates were considerably lower in CKD compared to dialysis patients, but remained higher than in transplanted patients (**Figure 2**).

Risk of Dialysis and Death in CKD

In CKD patients, both the analysis of time to death and time to dialysis were affected by the concurrent risk of starting dialysis or dying, respectively: older age was associated with an increased risk of death, but a decreased risk of dialysis progression (**Table 3**). When analysing death and dialysis as a composite outcome, age displayed a borderline association. Having an eGFR of <15 compared to 15-29 at inclusion was associated with an almost 3-fold increased risk of death or dialysis, while male sex was associated with a smaller risk increase, as was low compared to high education, and presence of comorbidity.

Mortality Compared to the General Population

Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.3-4.0) for CKD, 5.6 (95%CI 3.5-8.9) for transplanted, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis patients (**Figure 3**). Mortality hazard ratios were statistically significant for cardiovascular as well as non-cardiovascular deaths for all groups.

Mortality in Chronic Kidney Disease versus Renal Replacement Therapy

In a direct comparison of patients in different health states (conditioned on age, sex, diabetes status, education level, and index year), all groups differed significantly from each other in terms of mortality hazard: transplanted patients had the lowest risk, followed by patients with CKD stages 4 and 5,

peritoneal dialysis, and hemodialysis patients (**Table 4**; all P<.001). Compared to chronic kidney disease patients, peritoneal dialysis had a 1.7 (95%CI 1.4-2.1) and hemodialysis patients a 2.6 (95%CI 2.3-2.9) times greater mortality hazard.

Education Level and Mortality

9 years of education or less, compared to more than 12 years, was associated with an increased mortality hazard overall (hazard ratio 1.4, 95%CI 1.2-1.7; **Figure 4**). The hazard ratio point estimate for ≤9 years of education versus >12 years was elevated in all health states, but did not reach statistical significance in the smaller peritoneal dialysis and transplanted groups.

DISCUSSION

Principal Findings

In this population-based cohort study we did not find support for mortality in CKD to be similar to dialysis mortality. Relative age-adjusted mortality was lowest in the transplanted group followed by CKD, peritoneal dialysis, and hemodialysis. Compared to dialysis patients, CKD patients had lower absolute mortality in age-adjusted analyses, lower relative mortality versus the general population, and lower relative mortality in direct comparison.

Strengths & Weaknesses

This study was population-based, and data were collected in routine clinical care to which there is universal access in Sweden. No restrictions were set regarding demography or comorbidities, increasing generalizability. Another strength was that we followed patients from CKD to death directly, or via different forms of renal replacement therapy. We could estimate death rates in CKD stages 4 and 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same calendar period and at the same hospitals.

Using the unique personal identity number of each Swedish resident and linkage to national mortality data, follow-up was complete. Using national registers, we could also collect data on comorbidities, as well as match general population controls to each patient, which is likely to result in more accurate estimates than if using aggregated life-table data.

One limitation was that while all renal replacement therapy patients in Stockholm County were included, an unknown number of CKD patients were missed: CKD is under-diagnosed and many patients are identified only at dialysis start, or die before identification. Our results should therefore only be generalized to CKD patients in nephrology care.

Secondly, comparing mortality estimates in the respective health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the CKD health state.[16] Such channeling of survivors likely decreases the mortality differential between CKD and dialysis patients. To be selected for transplantation several prognostic factors are also considered, such as age and diabetes (which we adjusted for), but also general frailty (which we did not capture beyond certain comorbidities). Also, the lower mortality in peritoneal dialysis compared to hemodialysis should be interpreted with caution, as patients may transfer to hemodialysis at the end of life, inflating hemodialysis mortality estimates. Prognostic factors may also be worse for hemodialysis patients than in patients selected for peritoneal dialysis, although the groups were similar in terms of comorbidity status and education level. Other channeling variables may still influence relative mortality between the groups. Some observations could also support our finding of lower mortality in peritoneal dialysis than hemodialysis: data indicate that more frequent dialysis is beneficial,[17] and peritoneal dialysis does not seem to result in the same degree of myocardial stunning,[5] two factors that could contribute to lower mortality rates in peritoneal dialysis than in hemodialysis.

Finally, several important potential confounders were taken into account, such as age, sex, diabetes status, and education level, but residual confounding due to other risk factors cannot be ruled out. For example, ethnicity may affect mortality through various mechanisms, including access to renal transplantation (depending on blood group and tissue type histocompatibility). We did not have access to ethnicity data and could therefore not determine whether there was an imbalance between cases and controls. The analyses were also limited by lack of albuminuria data.

Previous Research

Go et al[1] analysed 8458 insured CKD stage 4 and 5 patients with similar mean age as in our study, and similar prevalence of diabetes. Their sample was predominantly female compared to only 35% women in our study. They found age-standardised death rates of 11 and 14 per 100 person-years in CKD stage 4 and 5, respectively, approaching the levels seen in dialysis. The death rates were standardised to their full study population which was comparatively young (mean age 52 years), complicating comparisons of absolute mortality rates with our study (mean age 66 years). They reported adjusted mortality hazard ratios of 3.2 and 5.9 for the two groups versus insured patients with eGFR≥60.

In a meta-analysis of more than 100,000 patients, Matsushita et al[4] used eGFR 90-104 as reference and found mortality hazard ratios for CKD stage 4 patients between 4 and 7 over a range of urine albumin-to-creatinine ratios. Our findings for CKD stage 4 and 5, versus matched general population controls, seem largely congruent with both these previous studies, but appear lower than the standardised mortality ratio of 8.3 reported by Evans et al from Sweden.[2] This discrepancy is most likely explained by their exclusion of patients ≥75 years old (a patient segment making up 33% of our sample in the current study), as relative mortality compared to the general population decreases with age, pushing our estimates downwards compared to Evans et al's.

Regarding dialysis mortality, we found both cardiovascular and non-cardiovascular mortality to be elevated, similar to findings from a large European analysis of dialysis mortality by de Jager et al.[3] They analysed all dialysis patients as a group, while we separated peritoneal dialysis and hemodialysis patients (for which we found differential mortality).

We also found an association between education level and CKD progression, as well as survival in renal replacement therapy. This is in agreement with Swedish findings regarding risk factors for chronic renal failure (unskilled workers versus professionals),[18] and a Danish study on risk of renal replacement therapy (low versus high income families, and low versus high education level).[19]

Implications

As mortality increases after both peritoneal and hemodialysis initiation, optimal timing of dialysis start has been debated, particularly as dialysis is initiated at higher eGFR today than previously: in the United States in 1996 only 4% started dialysis with eGFR>15, while 15% did in 2005.[20] The trend has been similar in Europe.[21] A recent randomized controlled trial gave no indication that early start was beneficial for survival.[22] Our data showing much higher mortality in both peritoneal dialysis and hemodialysis compared to CKD, together with previous findings, indicate that caution should be exercised before initiating dialysis.

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Competing interest statement
JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors
MN, SHJ, CGE, and BH conceived the study hypothesis. MN and JE conducted the statistical analyses. MN wrote the first draft of the manuscript. MN, SHJ, JE, CGE, and BH critically reviewed and contributed to the final draft. All authors are guarantors.

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BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

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Table 1 Participant characteristics at chronic kidney disease register inclusion, start of dialysis or transplantation[a]

	Chronic Kidney Disease			Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
	Stage 4	Stage 5	Stages 4 & 5			
N	2041	999	3040	725	1791	606
Sex (% men)	1389 (68%)	586 (59%)	1975 (65%)	461 (64%)	1130 (63%)	387 (64%)
Age (Years)						
Mean (SD)	67 (15)	65 (15)	66 (15)	60 (15)	62 (15)	48 (12)
Median (25^{th}-75^{th})	70 (58-78)	68 (56-77)	69 (58-78)	62 (51-72)	65 (54-75)	50 (39-58)
n (%)						
18-49y	288 (14%)	164 (16%)	452 (15%)	165 (23%)	353 (20%)	310 (51%)
50-59y	289 (14%)	158 (16%)	447 (15%)	169 (23%)	324 (18%)	187 (31%)
60-69y	457 (22%)	217 (22%)	674 (22%)	187 (26%)	446 (25%)	107 (18%)
≥70y	1007 (49%)	460 (46%)	1467 (48%)	204 (28%)	668 (37%)	2 (0%)
Education[b]						
≤9y	370 (28%)	211 (30%)	581 (29%)	153 (26%)	414 (31%)	127 (21%)
10-12y	565 (42%)	276 (40%)	841 (41%)	240 (40%)	546 (41%)	255 (42%)
>12y	361 (27%)	162 (23%)	523 (26%)	177 (30%)	275 (20%)	212 (35%)
Missing	35 (3%)	49 (7%)	84 (4%)	26 (4%)	112 (8%)	12 (2%)
Comorbidity[c]						
Diabetes	778 (38%)	311 (31%)	1 089 (36%)	229 (32%)	634 (35%)	134 (22%)
Malignancies	355 (17%)	156 (16%)	511 (17%)	91 (13%)	319 (18%)	29 (5%)
Circulatory Disease	1678 (82%)	739 (74%)	2417 (80%)	598 (82%)	1484 (83%)	461 (76%)
Hypertension	1391 (68%)	613 (61%)	2004 (66%)	517 (71%)	1193 (67%)	402 (66%)
Cardiovascular Disease	946 (46%)	379 (38%)	1325 (44%)	297 (41%)	867 (48%)	147 (24%)
Myocardial Infarction[d]	276 (14%)	117 (12%)	393 (13%)	93 (13%)	236 (13%)	21 (3%)
Stroke	228 (11%)	117 (12%)	345 (11%)	64 (9%)	185 (10%)	27 (4%)
COPD[e]	133 (7%)	55 (6%)	188 (6%)	32 (4%)	121 (7%)	11 (2%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or sub-diagnosis of the respective ICD-codes used (specified in **eTable 1**)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

Table 2 Mortality and accumulated person-years by health state[a]

	Chronic Kidney Disease Stage 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
N	3040	725	1791	606
Person-Years	**6553**	**1113**	**3680**	**2935**
Mean (SD)	2.2 (1.7)	1.5 (1.4)	2.1 (2.2)	4.8 (3.2)
Median (25^{th}-75^{th} Percentile)	1.7 (0.8-3.2)	1.1 (0.5-2.3)	1.3 (0.4-3.0)	4.6 (2.1-7.4)
Deaths (1999-2010)	**766**	**186**	**924**	**53**
Circulatory Deaths (1999-2008)[b]	381 (76%)	128 (85%)	513 (69%)	26 (67%)
Deaths/1000 Person-Years (95%CI)				
Patients	117 (109-125)	167 (145-193)	251 (235-268)	18 (14-24)
Matched General Population Controls[c]	51 (48-54)	21 (17-26)	20 (18-22)	4 (3-5)

[a] SD=standard deviation

[b] Causes of death not available for deaths occurring in 2009 and 2010 (530/1929 deaths; 27%). Cardiovascular causes determined from main *and* contributory diagnoses.

[c] Matched 5:1 by age, sex, and index year

Table 3 Adjusted hazard ratios for risk of progressing to dialysis, death, and death or dialysis for chronic kidney disease 4 and 5 patients (conditioned on index year; n=3040)

	Adjusted Hazard Ratio (95%CI)		
	Dialysis	**Death**	**Death or Dialysis**
eGFR[a]<15	3.98 (3.47-4.56) P<.001	1.62 (1.37-1.92) P<.001	2.75 (2.48-3.04) P<.001
eGFR[a] 15-29 (reference)	1.0	1.0	1.0
Demography			
Male	1.13 (0.99-1.28) P=.06	1.15 (0.98-1.34) P=.08	1.14 (1.03-1.25) P=.01
Female (reference)	1.0	1.0	1.0
Age			
18-49y	1.29 (1.07-1.56) P=.009	0.31 (0.15-0.65) P=.002	1.19 (0.99-1.42) P=.06
50-59y (reference)	1.0	1.0	1.0
60-69y	0.98 (0.81-1.18) P=.84	2.36 (1.65-3.39) P<.001	1.16 (0.99-1.36) P=.07
≥70y	0.73 (0.60-0.88) P=.001	3.42 (2.43-4.80) P<.001	1.17 (1.00-1.37) P=.05
Education Level			
≤9y	1.12 (0.93-1.35) P=.2	1.43 (1.08-1.90) P=.01	1.21 (1.04-1.41) P=.01
10-12y	1.09 (0.92-1.30) P=.3	1.24 (0.93-1.64) P=.1	1.15 (0.99-1.33) P=.06
>12y (reference)	1.0	1.0	1.0
Comorbidity			
Diabetes	1.31 (1.15-1.49) P<.001	1.26 (1.08-1.46) P=.003	1.30 (1.18-1.43) P<.001
Circulatory Disease	1.15 (0.99-1.33) P=.06	1.59 (1.27-2.00) P<.001	1.23 (1.09-1.39) P=.001
Malignancy	1.03 (0.88-1.21) P=.69	1.50 (1.29-1.75) P<.001	1.24 (1.11-1.38) P<.001
Events	**1075**	**766**	**1841**
Person-Years[b]	**6553**	**6553**	**6553**

[a] Estimated glomerular filtration rate (using the MDRD formula; ml/min/1.73m^2)

[b] Patients censored at time of death, transition to another health state or end of follow-up, whichever came first. Failures in chronic kidney disease include only deaths occurring while patients are in the chronic kidney disease health state, not deaths occurring after switching to renal replacement therapy.

Table 4 Conditional[a] mortality hazard ratios for chronic kidney disease 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients compared to each other

	Mortality hazard ratios (95%CI)			
	Chronic kidney disease 4 & 5	**Peritoneal dialysis**	**Hemo-dialysis**	**Transplantation**
Chronic kidney disease stage 4 & 5	1.0	1.7 (1.4-2.1) P<.001	2.6 (2.3-2.9) P<.001	0.5 (0.3-0.7) P<.001
Peritoneal dialysis	0.6 (0.5-0.7) P<.001	1.0	1.5 (1.2-1.8) P<.001	0.3 (0.2-0.4) P<.001
Hemodialysis	0.4 (0.3-0.4) P<.001	0.7 (0.6-0.8) P<.001	1.0	0.2 (0.1-0.3) P<.001
Transplantation	2.1 (1.5-3.0) P<.001	3.6 (2.5-5.3) P<.001	5.3 (3.7-7.6) P<.001	1.0
N	**3040**	**725**	**1791**	**606**
Deaths	**766**	**186**	**924**	**53**
Person-Years	**6553**	**1113**	**3680**	**2935**

[a] Models conditioned on age (18-49y, 50-59y, 60-69y, ≥70y), sex, education level (≤9y, 10-12y, >12y), diabetes, and index year

FIGURE LEGENDS

Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis and transplanted patients, as well as matched general population controls

Figure 2 Crude mortality rates by health state and age

Figure 3 Conditional all cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls

Figure 4 Mortality hazard ratios by education level using >12 years of education as reference

Mortality in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

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ABSTRACT (300 words)

Objective: To compare mortality in chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min/1.73m^2), peritoneal dialysis, hemodialysis, and transplanted patients.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Swedish adult patients with chronic kidney disease stage 4 or 5 (n=3040; mean age 66y), peritoneal dialysis (n=725; 60y), hemodialysis (n=1791; 62y), and renal transplantation (n=606; 48y) were identified in Stockholm County clinical quality registers for renal disease between 1999 and 2010. Five general population controls were matched to each patient by age, sex, and index year.

Exposure: Chronic kidney disease status (stage 4 or 5/peritoneal dialysis/hemodialysis/ transplanted)

Primary Outcome: All cause mortality ascertained from the Swedish Causes of Death Register. Mortality hazard ratios were estimated using Cox regression conditioned on age, sex, diabetes status, education level, and index year.

Results: During 6553 person-years 766 patients with chronic kidney disease stage 4 or 5 died (deaths/100 person-years 12, 95%CI 11-13) compared with 186 deaths during 1113 person-years in peritoneal dialysis (17, 95%CI 15-19), 924 deaths during 3680 person-years in hemodialysis (25, 95%CI 23-27), and 53 deaths during 2935 person-years in transplanted patients (1.8, 95%CI 1.4-2.4). Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.2-4.0) for chronic kidney disease, 5.6 (95%CI 3.5-8.9) for transplanted patients, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis. In direct comparison versus chronic kidney disease, the mortality hazard ratio was 1.7 (95%CI 1.4-2.1) for peritoneal dialysis, 2.6 (95%CI 2.3-2.9) for hemodialysis, and 0.5 (95%CI 0.3-0.7) for transplanted patients.

Conclusion: We did not find support for mortality in CKD to be similar to dialysis mortality. Patients with chronic kidney disease stage 4 or 5 had considerably lower mortality risk than dialysis patients, and considerably higher risk than transplanted patients and matched general population controls.

ARTICLE FOCUS

- Chronic kidney disease and renal replacement therapy are associated with increased mortality
- Some studies suggest mortality in chronic kidney disease stage 4 and 5 to approach dialysis mortality rates
- No studies have compared mortality in chronic kidney disease, in different forms of dialysis, and after transplantation with the general population, and directly with each other

KEY MESSAGES

- Relative mortality risk versus matched general population controls was 4 in chronic kidney disease, 6 in transplanted patients, 9 in peritoneal dialysis and 13 in hemodialysis patients
- In direct comparison versus chronic kidney disease patients, relative mortality risk was 0.5 in transplanted patients, 1.7 in peritoneal dialysis, and 2.6 in hemodialysis
- The markedly increased mortality observed in both peritoneal dialysis and hemodialysis suggests that such therapies should not be started too early

STRENGTHS & LIMITATIONS

- This study was population-based with no restrictions regarding age or comorbidities, and data were collected in routine clinical care to which there is universal access in Sweden
- Using the unique personal identity number of each Swedish resident, follow-up was complete regarding mortality
- Although all renal replacement therapy patients in the catchment area were included, an unknown number of chronic kidney disease stage 4 and 5 patients were missed, as the condition is underdiagnosed
- Direct comparison of mortality across different health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the chronic kidney disease health state

INTRODUCTION

Mortality is substantially elevated in chronic kidney disease (CKD) and dialysis patients,[1-3] with some studies describing CKD patients in stages 4 and 5 (estimated glomerular filtration rate [eGFR] 15-29 and <15 ml/min/1.73m^2, respectively) as having mortality rates approaching the rates in dialysis.[1] However, there are no studies directly quantifying the relative mortality in CKD, dialysis (separating peritoneal and hemodialysis), and transplanted patients.

An analysis of an insured US population found patients in CKD stages 4 and 5 to approach dialysis mortality rates with a 3- and 6-fold higher mortality risk, respectively, than patients with eGFR ≥60.[1] This can be compared with a standardised mortality ratio of 8 reported in Swedish incident CKD patients stages 4 and 5 followed for up to almost 7 years,[2] and with hazard ratios ranging from 3.7 to 7.0 for stage 4 patients (eGFR 15-29) with varying levels of albumin-to-creatinine-ratio in a meta-analysis of more than 100,000 patients, using patients with an eGFR of 90-104 as reference.[4]

Regarding dialysis mortality, a large European study showed an 8-fold higher age-standardised mortality due to both cardiovascular and non-cardiovascular death compared to the general population.[3] The study did not distinguish between peritoneal dialysis and hemodialysis.

These US and European studies indicate that mortality in CKD stages 4 and 5 may be as high as in dialysis. However, control groups differed between the studies (patients with normal kidney function defined as eGFR ≥60[1] or 90-104[4]; aggregated Swedish[2] or European life tables[3]), and mortality may differ between modes of dialysis.[5]

The aim of this population-based cohort study was to examine mortality in CKD stages 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients in relation to matched general population controls, and directly with each other.

METHODS

This population-based cohort study was performed in the Swedish health care system using patient data from clinical quality registers kept for quality of care evaluation in Stockholm County. These data sources were combined with matched general population controls, and enriched with outcome and exposure data via linkage to nationwide health registers kept by the National Board of Health & Welfare and demographic registers at Statistics Sweden. Register linkage was performed using the unique personal identity number assigned to each Swedish resident.[6] Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 9.4 million on December 31, 2010 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 2.1 million inhabitants, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, and patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient hospital care.[7] Care for CKD patients was a mix of mainly outpatient hospital and primary care. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[8] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[9] and the corresponding European guidelines.[10]

Quality Register Sources

CKD Patients: Data from the Stockholm County CKD Register were used, including adult CKD patients in stages 4 and 5 not on dialysis registered at Karolinska and Danderyd University Hospital from 1999 to 2010 in the outpatient setting. This does not include all CKD stage 4 and 5 patients in the county, as some get care elsewhere and some remain undetected. Stages 4 and 5 were defined as an eGFR of 15-29 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[11] Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed.

Renal Replacement Therapy Patients: Data on dialysis initiation, type of dialysis, and transplantation were collected from the Swedish Register of Renal Replacement Therapy, including all adult patients on renal replacement therapy in Stockholm County.[12 13]

The National Patient Register

Data on inpatient and outpatient hospital care were retrieved from the Swedish National Patient Register.[14] This register contains the personal identity number, visit/admission date (and discharge date for inpatients), and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10). The register reached national coverage in 1987 for inpatient care, and the outpatient component was added in 2001.

From inpatient and outpatient care registered in the National Patient Register, data on hospital visits listing diabetes, malignancies, circulatory disease, and chronic obstructive pulmonary disease were gathered. Visits listing these diagnoses were searched for during the last ten years (ICD-9 and ICD-10 codes provided in **eTable 1**).

Matched General Population Control Cohort

From the Register of the Total Population at Statistics Sweden, up to five general population controls were matched to each patient at the time of inclusion into the CKD register, and renal replacement therapy initiation, using age (+/-1 year), sex, and index year as matching factors. Data on emigration status and highest attained education were also retrieved from Statistics Sweden.

Outcome and Follow-Up

The primary outcome was all cause mortality. Secondary outcomes for CKD patients included initiation of renal replacement therapy and the composite outcome death or dialysis.

Dates and causes of death were retrieved from the Causes of Death Register kept by the National Board of Health and Welfare. Dates of death were available until July 31, 2010, while main and contributory death causes were available until December 31, 2008.

CKD and renal replacement therapy patients included from January 1, 1999, were analysed. Follow-up started at date of inclusion into the Stockholm CKD Register, dialysis initiation, or transplantation. Patients accrued person-time in a specific health state until death, transition to another health state, emigration, or July 31, 2010, whichever came first.

Statistical Analysis

Unadjusted incidence rates and Kaplan-Meier curves were used to present absolute risks. For CKD patients, a Cox proportional hazards model was used to model time to dialysis, and the composite outcome death or dialysis. The models were adjusted for age, sex, education level (≤9, 10-12, >12 years, missing), baseline eGFR (stage 4 versus 5), and comorbidity status, and index year.

Comparison versus the General Population: In mortality analyses versus matched general population controls, Cox models conditioned on age, sex, education level, diabetes status, and index year were used. Some patients did not have a full five controls, but were still included in the analyses, while patients with no controls were excluded. For dialysis and transplanted patients the Andersen-Gill[15] method was applied allowing for patients to re-enter a health state after exiting.

In order to investigate whether potential differences in all-cause mortality were driven by cardiovascular mortality, sensitivity analyses were performed for cardiovascular as well as non-cardiovascular deaths. An analysis was also performed to compare mortality by education level.

Direct Comparison of CKD versus Renal Replacement Therapy: To directly compare mortality in the different health states, a Cox model conditioned on age, sex, education level, diabetes status, and index year was used with health state as primary predictor.

Missing data on education level were handled using the missing indicator method. Data were complete on age, sex, and register-determined comorbidity status. Missing baseline eGFR resulted in exclusion from CKD analyses.

Statistical analyses were performed using SAS (version 9.3) and Stata (version 11). All P-values are two-sided and P-values <.05 were considered statistically significant.

RESULTS

A total of 4249 patients were included. Follow-up of mortality was complete and all patients were analysed, except for 19 CKD patients who were excluded due to missing baseline eGFR.

Patient characteristics at inclusion, dialysis initiation and transplantation are shown in **Table 1**. CKD patients were on average 66 years old at inclusion, while dialysis patients were younger, and transplanted patients much younger: 48% of CKD patients were more than 70 years old, compared to 37% of hemodialysis, 28% of peritoneal dialysis, and 0% of the transplanted patients. All groups were predominantly male, and the education level was broadly similar to that in the general population.

Regarding selected register-identified comorbidities, the CKD and dialysis patients were similar, while the younger transplanted group displayed much lower prevalence. More than 30% of patients (except the transplanted group) had diabetes, compared to 3-7% in the matched general population (**eTable 2**). Approximately 80% of patients had circulatory disease history at inclusion, with about 10% having had myocardial infarction and 10% stroke (except transplanted patients). In CKD and dialysis patients malignancies were also more common than in the general population.

In the CKD cohort at inclusion, the mean eGFR was 18 (SD 6; median 18; range 4.1-29.9). A third (n=999) had values <15, while 67% (n=2041) had values between 15 and 29 (full distribution shown in **eFigure**).

Observation Time and Deaths

Crude death rates were highest in hemodialysis and lowest in transplanted patients (**Table 2; Figure 1**). When stratified by age, crude mortality rates were considerably lower in CKD compared to dialysis patients, but remained higher than in transplanted patients (**Figure 2**).

Risk of Dialysis and Death in CKD

In CKD patients, both the analysis of time to death and time to dialysis were affected by the concurrent risk of starting dialysis or dying, respectively: older age was associated with an increased risk of death, but a decreased risk of dialysis progression (**Table 3**). When analysing death and dialysis as a composite outcome, age displayed a borderline association. Having an eGFR of <15 compared to 15-29 at inclusion was associated with an almost 3-fold increased risk of death or dialysis, while male sex was associated with a smaller risk increase, as was low compared to high education, and presence of comorbidity.

Mortality Compared to the General Population

Versus matched general population controls, the mortality hazard ratio was 3.6 (95%CI 3.3-4.0) for CKD, 5.6 (95%CI 3.5-8.9) for transplanted, 9.2 (95%CI 6.6-12.7) for peritoneal dialysis, and 12.6 (95%CI 10.8-14.6) for hemodialysis patients (**Figure 3**). Mortality hazard ratios were statistically significant for cardiovascular as well as non-cardiovascular deaths for all groups.

Mortality in Chronic Kidney Disease versus Renal Replacement Therapy

In a direct comparison of patients in different health states (conditioned on age, sex, diabetes status, education level, and index year), all groups differed significantly from each other in terms of mortality hazard: transplanted patients had the lowest risk, followed by patients with CKD stages 4 and 5,

peritoneal dialysis, and hemodialysis patients (**Table 4**; all P<.001). Compared to chronic kidney disease patients, peritoneal dialysis had a 1.7 (95%CI 1.4-2.1) and hemodialysis patients a 2.6 (95%CI 2.3-2.9) times greater mortality hazard.

Education Level and Mortality

9 years of education or less, compared to more than 12 years, was associated with an increased mortality hazard overall (hazard ratio 1.4, 95%CI 1.2-1.7; **Figure 4**). The hazard ratio point estimate for ≤9 years of education versus >12 years was elevated in all health states, but did not reach statistical significance in the smaller peritoneal dialysis and transplanted groups.

DISCUSSION

Principal Findings

In this population-based cohort study we did not find support for mortality in CKD to be similar to dialysis mortality. Relative age-adjusted mortality was lowest in the transplanted group followed by CKD, peritoneal dialysis, and hemodialysis. Compared to dialysis patients, CKD patients had lower absolute mortality in age-adjusted analyses, lower relative mortality versus the general population, and lower relative mortality in direct comparison.

Strengths & Weaknesses

This study was population-based, and data were collected in routine clinical care to which there is universal access in Sweden. No restrictions were set regarding demography or comorbidities, increasing generalizability. Another strength was that we followed patients from CKD to death directly, or via different forms of renal replacement therapy. We could estimate death rates in CKD stages 4 and 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same calendar period and at the same hospitals.

Using the unique personal identity number of each Swedish resident and linkage to national mortality data, follow-up was complete. Using national registers, we could also collect data on comorbidities, as well as match general population controls to each patient, which is likely to result in more accurate estimates than if using aggregated life-table data.

One limitation was that while all renal replacement therapy patients in Stockholm County were included, an unknown number of CKD patients were missed: CKD is under-diagnosed and many patients are identified only at dialysis start, or die before identification. Our results should therefore only be generalized to CKD patients in nephrology care.

Secondly, comparing mortality estimates in the respective health states is complicated by channeling issues, as patients in renal replacement therapy are required to have survived the CKD health state.[16] Such channeling of survivors likely decreases the mortality differential between CKD and dialysis patients. To be selected for transplantation several prognostic factors are also considered, such as age and diabetes (which we adjusted for), but also general frailty (which we did not capture beyond certain comorbidities). Also, the lower mortality in peritoneal dialysis compared to hemodialysis should be interpreted with caution, as patients may transfer to hemodialysis at the end of life, inflating hemodialysis mortality estimates. Prognostic factors may also be worse for hemodialysis patients than in patients selected for peritoneal dialysis, although the groups were similar in terms of comorbidity status and education level. Other channeling variables may still influence relative mortality between the groups. Some observations could also support our finding of lower mortality in peritoneal dialysis than hemodialysis: data indicate that more frequent dialysis is beneficial,[17] and peritoneal dialysis does not seem to result in the same degree of myocardial stunning,[5] two factors that could contribute to lower mortality rates in peritoneal dialysis than in hemodialysis.

Finally, several important potential confounders were taken into account, such as age, sex, diabetes status, and education level, but residual confounding due to other risk factors cannot be ruled out. For example, ethnicity may affect mortality through various mechanisms, including access to renal transplantation (depending on blood group and tissue type histocompatibility). We did not have access to ethnicity data and could therefore not determine whether there was an imbalance between cases and controls. The analyses were also limited by lack of albuminuria data.

Previous Research

Go et al[1] analysed 8458 insured CKD stage 4 and 5 patients with similar mean age as in our study, and similar prevalence of diabetes. Their sample was predominantly female compared to only 35% women in our study. They found age-standardised death rates of 11 and 14 per 100 person-years in CKD stage 4 and 5, respectively, approaching the levels seen in dialysis. The death rates were standardised to their full study population which was comparatively young (mean age 52 years), complicating comparisons of absolute mortality rates with our study (mean age 66 years). They reported adjusted mortality hazard ratios of 3.2 and 5.9 for the two groups versus insured patients with eGFR≥60.

In a meta-analysis of more than 100,000 patients, Matsushita et al[4] used eGFR 90-104 as reference and found mortality hazard ratios for CKD stage 4 patients between 4 and 7 over a range of urine albumin-to-creatinine ratios. Our findings for CKD stage 4 and 5, versus matched general population controls, seem largely congruent with both these previous studies, but appear lower than the standardised mortality ratio of 8.3 reported by Evans et al from Sweden.[2] This discrepancy is most likely explained by their exclusion of patients ≥75 years old (a patient segment making up 33% of our sample in the current study), as relative mortality compared to the general population decreases with age, pushing our estimates downwards compared to Evans et al's.

Regarding dialysis mortality, we found both cardiovascular and non-cardiovascular mortality to be elevated, similar to findings from a large European analysis of dialysis mortality by de Jager et al.[3] They analysed all dialysis patients as a group, while we separated peritoneal dialysis and hemodialysis patients (for which we found differential mortality).

We also found an association between education level and CKD progression, as well as survival in renal replacement therapy. This is in agreement with Swedish findings regarding risk factors for chronic renal failure (unskilled workers versus professionals),[18] and a Danish study on risk of renal replacement therapy (low versus high income families, and low versus high education level).[19]

Implications

As mortality increases after both peritoneal and hemodialysis initiation, optimal timing of dialysis start has been debated, particularly as dialysis is initiated at higher eGFR today than previously: in the United States in 1996 only 4% started dialysis with eGFR>15, while 15% did in 2005.[20] The trend has been similar in Europe.[21] A recent randomized controlled trial gave no indication that early start was beneficial for survival.[22] Our data showing much higher mortality in both peritoneal dialysis and hemodialysis compared to CKD, together with previous findings, indicate that caution should be exercised before initiating dialysis.

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Competing interest statement
JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors
MN, SHJ, CGE, and BH conceived the study hypothesis. MN and JE conducted the statistical analyses. MN wrote the first draft of the manuscript. MN, SHJ, JE, CGE, and BH critically reviewed and contributed to the final draft. All authors are guarantors.

Ethical approval
Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden (DNR: 2009/1225-31/5).

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BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

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Table 1 Participant characteristics at chronic kidney disease register inclusion, start of dialysis or transplantation[a]

	Chronic Kidney Disease			Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
	Stage 4	Stage 5	Stages 4 & 5			
N	2041	999	3040	725	1791	606
Sex (% men)	1389 (68%)	586 (59%)	1975 (65%)	461 (64%)	1130 (63%)	387 (64%)
Age (Years)						
Mean (SD)	67 (15)	65 (15)	66 (15)	60 (15)	62 (15)	48 (12)
Median (25^{th}-75^{th})	70 (58-78)	68 (56-77)	69 (58-78)	62 (51-72)	65 (54-75)	50 (39-58)
n (%)						
18-49y	288 (14%)	164 (16%)	452 (15%)	165 (23%)	353 (20%)	310 (51%)
50-59y	289 (14%)	158 (16%)	447 (15%)	169 (23%)	324 (18%)	187 (31%)
60-69y	457 (22%)	217 (22%)	674 (22%)	187 (26%)	446 (25%)	107 (18%)
≥70y	1007 (49%)	460 (46%)	1467 (48%)	204 (28%)	668 (37%)	2 (0%)
Education[b]						
≤9y	370 (28%)	211 (30%)	581 (29%)	153 (26%)	414 (31%)	127 (21%)
10-12y	565 (42%)	276 (40%)	841 (41%)	240 (40%)	546 (41%)	255 (42%)
>12y	361 (27%)	162 (23%)	523 (26%)	177 (30%)	275 (20%)	212 (35%)
Missing	35 (3%)	49 (7%)	84 (4%)	26 (4%)	112 (8%)	12 (2%)
Comorbidity[c]						
Diabetes	778 (38%)	311 (31%)	1 089 (36%)	229 (32%)	634 (35%)	134 (22%)
Malignancies	355 (17%)	156 (16%)	511 (17%)	91 (13%)	319 (18%)	29 (5%)
Circulatory Disease	1678 (82%)	739 (74%)	2417 (80%)	598 (82%)	1484 (83%)	461 (76%)
Hypertension	1391 (68%)	613 (61%)	2004 (66%)	517 (71%)	1193 (67%)	402 (66%)
Cardiovascular Disease	946 (46%)	379 (38%)	1325 (44%)	297 (41%)	867 (48%)	147 (24%)
Myocardial Infarction[d]	276 (14%)	117 (12%)	393 (13%)	93 (13%)	236 (13%)	21 (3%)
Stroke	228 (11%)	117 (12%)	345 (11%)	64 (9%)	185 (10%)	27 (4%)
COPD[e]	133 (7%)	55 (6%)	188 (6%)	32 (4%)	121 (7%)	11 (2%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or sub-diagnosis of the respective ICD-codes used (specified in **eTable 1**)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

Table 2 Mortality and accumulated person-years by health state[a]

	Chronic Kidney Disease Stage 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Trans-planted
N	3040	725	1791	606
Person-Years	**6553**	**1113**	**3680**	**2935**
Mean (SD)	2.2 (1.7)	1.5 (1.4)	2.1 (2.2)	4.8 (3.2)
Median (25^{th}-75^{th} Percentile)	1.7 (0.8-3.2)	1.1 (0.5-2.3)	1.3 (0.4-3.0)	4.6 (2.1-7.4)
Deaths (1999-2010)	**766**	**186**	**924**	**53**
Circulatory Deaths (1999-2008)[b]	381 (76%)	128 (85%)	513 (69%)	26 (67%)
Deaths/1000 Person-Years (95%CI)				
Patients	117 (109-125)	167 (145-193)	251 (235-268)	18 (14-24)
Matched General Population Controls[c]	51 (48-54)	21 (17-26)	20 (18-22)	4 (3-5)

[a] SD=standard deviation

[b] Causes of death not available for deaths occurring in 2009 and 2010 (530/1929 deaths; 27%). Cardiovascular causes determined from main *and* contributory diagnoses.

[c] Matched 5:1 by age, sex, and index year

Table 3 Adjusted hazard ratios for risk of progressing to dialysis, death, and death or dialysis for chronic kidney disease 4 and 5 patients (conditioned on index year; n=3040)

	Adjusted Hazard Ratio (95%CI)		
	Dialysis	Death	Death or Dialysis
eGFR[a]<15	3.98 (3.47-4.56) P<.001	1.62 (1.37-1.92) P<.001	2.75 (2.48-3.04) P<.001
eGFR[a] 15-29 (reference)	1.0	1.0	1.0
Demography			
Male	1.13 (0.99-1.28) P=.06	1.15 (0.98-1.34) P=.08	1.14 (1.03-1.25) P=.01
Female (reference)	1.0	1.0	1.0
Age			
18-49y	1.29 (1.07-1.56) P=.009	0.31 (0.15-0.65) P=.002	1.19 (0.99-1.42) P=.06
50-59y (reference)	1.0	1.0	1.0
60-69y	0.98 (0.81-1.18) P=.84	2.36 (1.65-3.39) P<.001	1.16 (0.99-1.36) P=.07
≥70y	0.73 (0.60-0.88) P=.001	3.42 (2.43-4.80) P<.001	1.17 (1.00-1.37) P=.05
Education Level			
≤9y	1.12 (0.93-1.35) P=.2	1.43 (1.08-1.90) P=.01	1.21 (1.04-1.41) P=.01
10-12y	1.09 (0.92-1.30) P=.3	1.24 (0.93-1.64) P=.1	1.15 (0.99-1.33) P=.06
>12y (reference)	1.0	1.0	1.0
Comorbidity			
Diabetes	1.31 (1.15-1.49) P<.001	1.26 (1.08-1.46) P=.003	1.30 (1.18-1.43) P<.001
Circulatory Disease	1.15 (0.99-1.33) P=.06	1.59 (1.27-2.00) P<.001	1.23 (1.09-1.39) P=.001
Malignancy	1.03 (0.88-1.21) P=.69	1.50 (1.29-1.75) P<.001	1.24 (1.11-1.38) P<.001
Events	**1075**	**766**	**1841**
Person-Years[b]	**6553**	**6553**	**6553**

[a] Estimated glomerular filtration rate (using the MDRD formula; ml/min/1.73m^2)

[b] Patients censored at time of death, transition to another health state or end of follow-up, whichever came first. Failures in chronic kidney disease include only deaths occurring while patients are in the chronic kidney disease health state, not deaths occurring after switching to renal replacement therapy.

Table 4 Conditional[a] mortality hazard ratios for chronic kidney disease 4 and 5, peritoneal dialysis, hemodialysis, and transplanted patients compared to each other

	Mortality hazard ratios (95%CI)			
	Chronic kidney disease 4 & 5	Peritoneal dialysis	Hemo-dialysis	Transplantation
Chronic kidney disease stage 4 & 5	1.0	1.7 (1.4-2.1) P<.001	2.6 (2.3-2.9) P<.001	0.5 (0.3-0.7) P<.001
Peritoneal dialysis	0.6 (0.5-0.7) P<.001	1.0	1.5 (1.2-1.8) P<.001	0.3 (0.2-0.4) P<.001
Hemodialysis	0.4 (0.3-0.4) P<.001	0.7 (0.6-0.8) P<.001	1.0	0.2 (0.1-0.3) P<.001
Transplantation	2.1 (1.5-3.0) P<.001	3.6 (2.5-5.3) P<.001	5.3 (3.7-7.6) P<.001	1.0
N	**3040**	**725**	**1791**	**606**
Deaths	**766**	**186**	**924**	**53**
Person-Years	**6553**	**1113**	**3680**	**2935**

[a] Models conditioned on age (18-49y, 50-59y, 60-69y, ≥70y), sex, education level (≤9y, 10-12y, >12y), diabetes, and index year

FIGURE LEGENDS

Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis and transplanted patients, as well as matched general population controls

Figure 2 Crude mortality rates by health state and age

Figure 3 Conditional all cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls

Figure 4 Mortality hazard ratios by education level using >12 years of education as reference

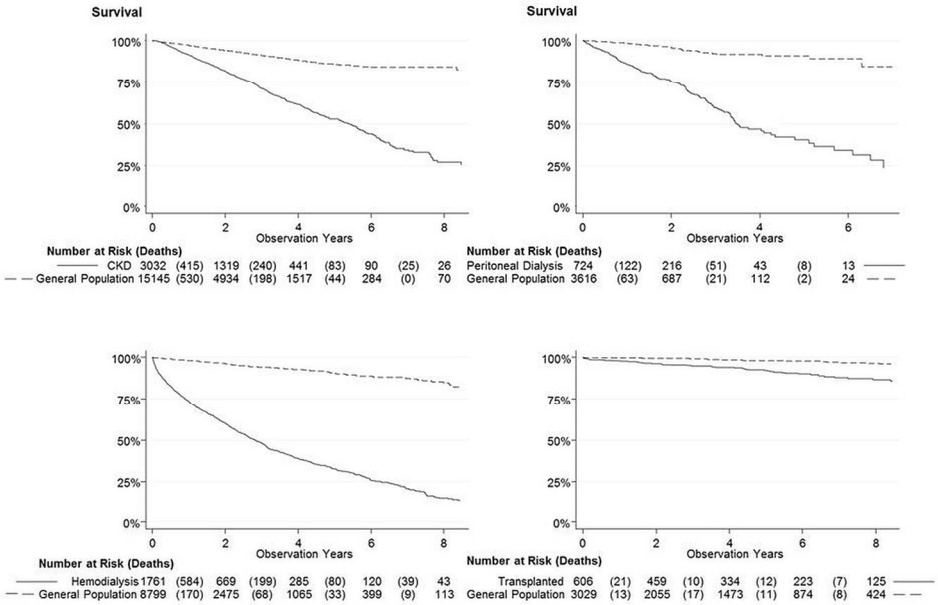


Figure 1 Survival curves describing time to death for chronic kidney disease patients (CKD), peritoneal dialysis, hemodialysis, and transplanted patients, as well as matched general population controls

120x90mm (300 x 300 DPI)

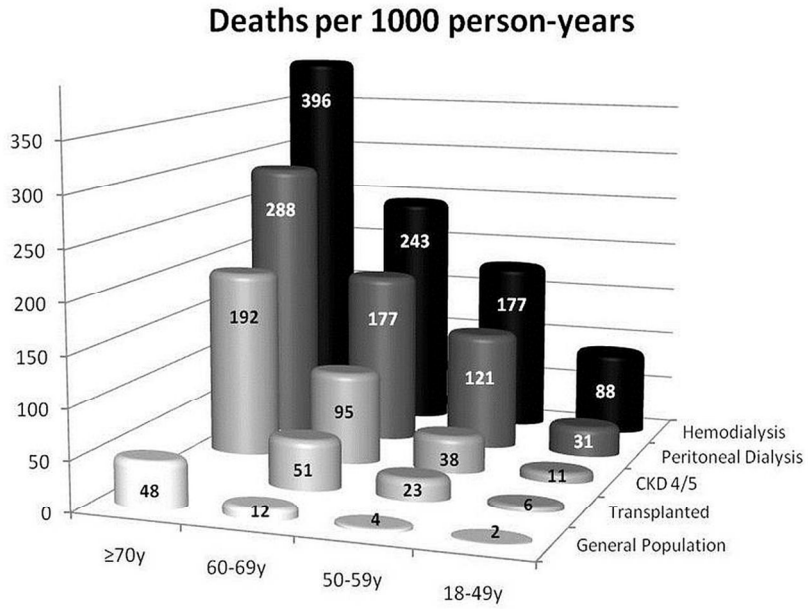


Figure 2 Crude mortality rates by health state and age

120x90mm (300 x 300 DPI)

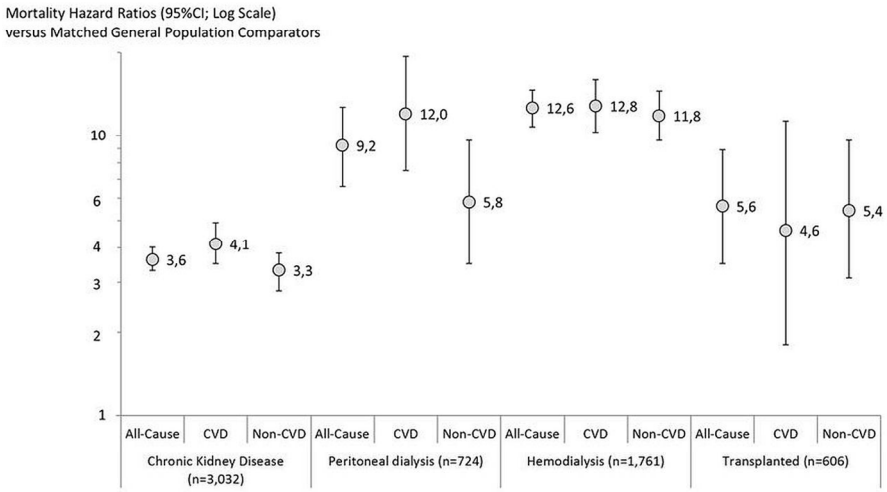


Figure 3 All cause, cardiovascular (CVD) and non-cardiovascular (non-CVD) mortality hazard ratios versus matched general population controls

121x90mm (300 x 300 DPI)

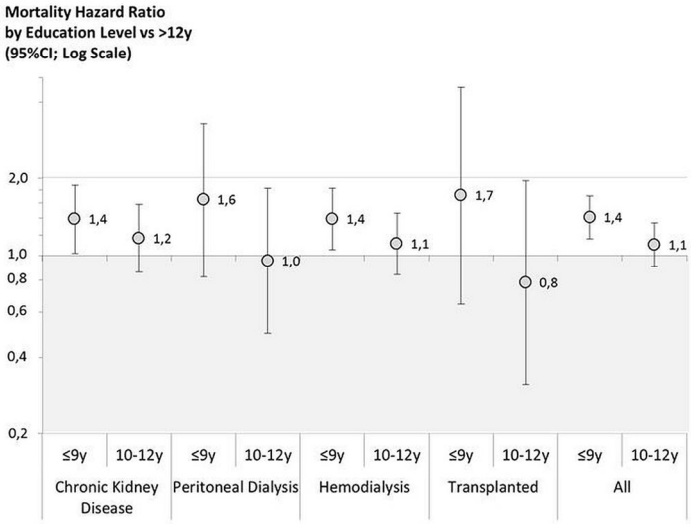


Figure 4 Mortality hazard ratios by education level using >12 years of education as reference

121x90mm (300 x 300 DPI)

Supplementary Web Appendix

Mortality in Chronic Kidney Disease & Renal Replacement Therapy:
A Population-Based Cohort Study

Martin Neovius (associate professor), Stefan H Jacobson (senior nephrologist, professor), Jonas Eriksson (doctoral student), Carl-Gustaf Elinder (senior nephrologist, professor) & Britta Hylander (senior nephrologist, associate professor)[4]

eTable 1 International Classification of Diseases (ICD) codes for comorbidities[a] and causes of death[b]

	ICD 10	ICD 9
Diabetes	E10-E11	250
Malignancies	C00-C99	140-208
Circulatory	I00-I99	390-459
Hypertension	I10-I15	401-405
Cardiovascular Disease	I20-I51	410-429
Myocardial Infarction	I21	410
Stroke	I60-I64	430-438
Lower-Extremity Deep Vein Thrombosis	I26, I80-I82	451-453, 415B
Chronic Obstructive Pulmonary Disease	J41-J44	490-492, 496
Uremia	N00-N19	580-599

[a] Comorbidities assessed from 10 years prior to the index year until the index year (1989 to 2010), i.e. both ICD 9 and ICD 10 codes used

[b] Deaths occurring from inclusion to end of follow-up (1999-2010), i.e. only ICD 10 codes used

eTable 2 Characteristics of matched general population controls (matched by age, sex, and index year)

General Population Controls	Chronic Kidney Disease 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplanted
N	**15,145**	**3616**	**8799**	**3029**
Education[a]				
≤9y	2534 (25%)	673 (23%)	1640 (25%)	587 (19%)
10-12y	4171 (41%)	1263 (43%)	2713 (41%)	1266 (42%)
>12y	3173 (31%)	951 (32%)	2077 (31%)	1110 (37%)
Missing	225 (2%)	66 (2%)	195 (3%)	66 (2%)
Comorbidity				
Diabetes	1037 (7%)	165 (5%)	495 (6%)	78 (3%)
Malignancies	1648 (11%)	270 (7%)	695 (8%)	84 (3%)
Circulatory	4813 (32%)	828 (23%)	2217 (25%)	309 (10%)
Hypertension	2279 (15%)	371 (10%)	973 (11%)	129 (4%)
Cardiovascular Disease	2907 (19%)	459 (13%)	1336 (15%)	126 (4%)
Myocardial Infarction[b]	634 (4%)	109 (3%)	266 (3%)	22 (1%)
Stroke	810 (5%)	131 (4%)	375 (4%)	30 (1%)
COPD[c]	508 (3%)	65 (2%)	221 (3%)	17 (1%)

[a] Education only available in patients <75y
[b] Subgroup of cardiovascular disease
[c] Chronic obstructive pulmonary disease

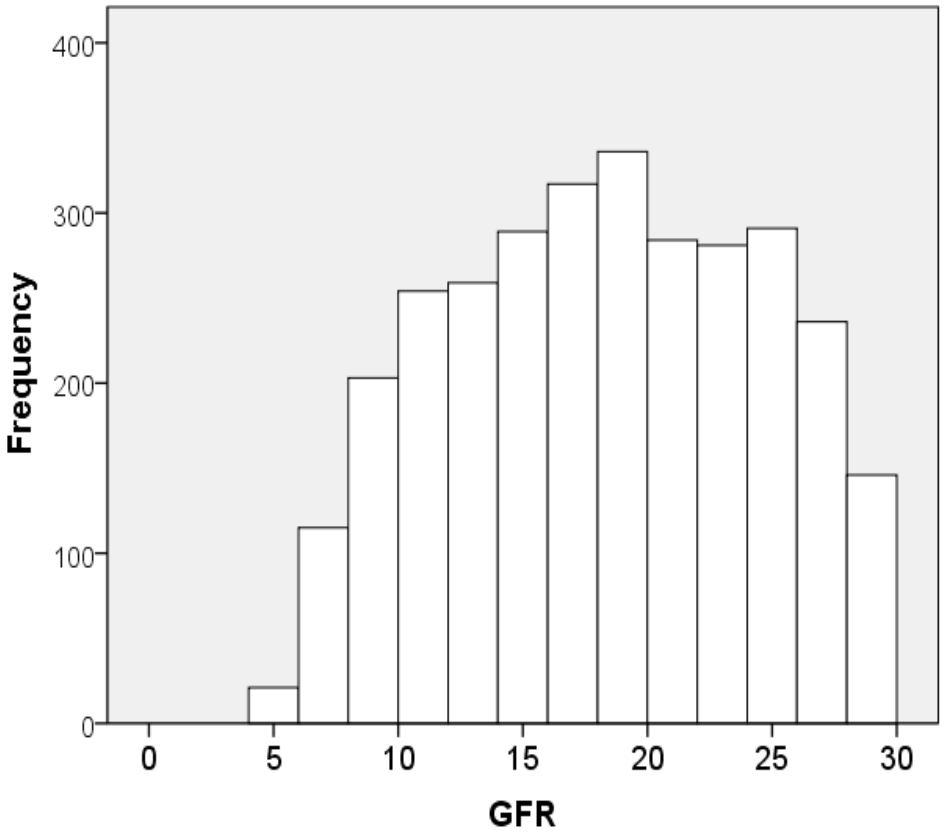
eTable 3 Underlying data for Figure 2

By Age	Chronic Kidney Disease4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplanted
N	**3040**	**725**	**1791**	**606**
Person-Years	**6553**	**1113**	**3680**	**2935**
18-49y	1002	227	725	1539
50-59y	1097	265	717	976
60-69y	1444	287	996	409
≥70y	3009	333	1240	9
Deaths (All Causes)	**766**	**186**	**924**	**53**
18-49y	9	7	64	10
50-59y	41	32	127	22
60-69y	137	51	242	21
≥70y	579	96	491	-
Deaths/100 Person-Years (95%CI)	**11.7 (10.9-12.5)**	**16.7 (14.5-19.3)**	**25.1 (23.5-26.8)**	**1.8 (1.4-2.4)**
18-49y	0.9 (0.5-1.7)	3.1 (1.5-6.5)	8.8 (6.9-11.3)	0.6 (0.3-1.2)
50-59y	3.7 (2.8-5.1)	12.1 (8.5-17.1)	17.7 (14.9-21.1)	2.3 (1.5-3.4)
60-69y	9.5 (8.0-11.2)	17.7 (13.5-23.3)	24.3 (21.4-27.6)	5.1 (3.3-7.9)
≥70y	19.2 (17.7-20.9)	28.8 (23.6-35.2)	39.6 (36.2-43.2)	-

eTable 4 Underlying data for Figure 3: Conditional[a] mortality hazard ratios for chronic kidney disease 4 and 5, peritoneal dialysis, hemodialysis and transplanted patients compared to matched general population controls

Patients vs Matched General Population Controls	Mortality Hazard Ratio (95%CI)			
	Chronic Kidney Disease 4 & 5	Peritoneal Dialysis	Hemo-Dialysis	Transplantation
All Cause	3.6 (3.2-4.0) P<.001	9.2 (6.6-12.7) P<.001	12.6 (10.8-14.6) P<.001	5.6 (3.5-8.9) P<.001
Cardiovascular Disease	4.1 (3.4-4.9) P<.001	12.0 (7.5-19.3) P<.001	12.8 (10.3-15.9) P<.001	4.6 (1.8-11.3) P=.001
Non-Cardiovascular Disease	3.2 (2.8-3.8) P<.001	5.8 (3.5-9.6) P<.001	11. 8 (9.6-14.5) P<.001	5.4 (3.1-9.6) P<.001
N				
Patients	3032	724	1761	606
Controls	15,145	3616	8799	3029
Deaths (All Cause)				
Patients	766	186	919	53
Controls	774	87	285	53
Person-Years				
Patients	6542	1109	3607	2936
Controls	25,652	4115	14,318	12,828
Data for patients and controls 1999-2008 (i.e. individuals with information on cause-specific mortality)				
N				
Patients	2482	627	1531	522
Controls	11,063	2909	7151	2319
Deaths (All Cause)				
Patients	707	170	871	50
Controls	670	75	266	51
Person-Years				
Patients	6164	1056	3441	2868
Controls	22,765	3693	13,160	12,137

[a]Models stratified by age, sex, education, diabetes, and index year (general population controls matched 5:1 by age, sex, and index year)



eFigure Distribution of estimated glomerular filtration rate (GFR; ml/min/1.73m^2) in patients with chronic kidney disease stage 4 and 5[a]

[a] Estimated using the MDRD formula

Recommended Format for the Reporting of Observational Cohort Studies According to the STROBE Group

Section	Item	Recommendation	Page
Title & Abstract	1	Indicate the study's design with a commonly used term in the title or the abstract.	1
		Provide in the abstract an informative and balanced summary of what was done and what was found.	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported.	4
Objectives	3	State specific objectives, including any prespecified hypotheses.	4
Methods			
Study design	4	Present key elements of study design early in the paper.	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection.	5-6
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow up.	5
		For matched studies, give matching criteria and number of exposed and unexposed.	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than 1 group.	5-6
Bias	9	Describe any efforts to address potential sources of bias.	5-6
Study size	10	Explain how the study size was arrived at.	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	6
Statistical methods	12	Describe all statistical methods, including those used to control for confounding.	6
		Describe any methods used to examine subgroups and interactions.	
		Explain how missing data were addressed.	
		If applicable, explain how loss to follow up was addressed.	
		Describe any sensitivity analyses.	
Results			
Participants	13*	Report numbers of individuals at each stage of study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analyzed.	7
		Give reasons for nonparticipation at each stage.	
		Consider use of a flow diagram.	
Descriptive data	14*	Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders.	7, 14
		Indicate number of participants with missing data for each variable of interest.	
		Summarize follow up time (eg, average and total amount).	
Outcome data	15*	Report numbers of outcome events or summary measures over time.	7-8 15-17
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included.	8
		Report category boundaries when continuous variables were categorized.	16-17
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	8
Discussion			
Key results	18	Summarize key results with reference to study objectives.	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalizability	21	Discuss the generalizability (external validity) of the study results.	9
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	11